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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 3 1950

VALVULOTOMY FOR MITRAL STENOSIS

REPORT OF SIX SUCCESSFUL CASES

BY

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It is now a quarter of a century since a number of attempts were made to relieve mitral stenosis by operation. The most sustained efforts to solve this problem by direct attack on the valves were made by Cutler and his associates (Cutler and Beck, 1929). Their first patient survived four years and was thought to have been improved; six others died soon after operation, as also did single cases reported by Allen and Graham (1922) and by Pribram (1926). Souttar (1925) alone has published a further success in an important paper from this country.

These early efforts were succeeded by a long period of inaction, and many thought that direct surgery of the valves of the heart was too dangerous to be practicable. The need for reconsidering this has become increasingly clear during recent years, because great advances in thoracic surgery and anaesthesia and in the aftercare of the patient have entirely changed the prospects of success. That successful operations for the direct relief of valvular stenosis are possible was shown in the case of the pulmonary valve (Brock, 1948); and that successful resection of infundibular stenosis was also possible was shown in the following year (Brock, 1949). We have performed in all over 45 direct operations on the heart for the relief of these types of stenosis.

While this work was being developed during the last four years our attention was also directed towards the relief of mitral stenosis by direct operation on the mitral valve. We are now able to report eight such cases, six of which are successful. These clinical results show that operation is not only possible but holds out hope of relief for a number of sufferers from this crippling condition.

That we have tried to select our cases with proper caution, recognizing the inherent dangers and difficulties, is shown by the fact that out of the many patients seen during this time only a few were specifically considered for surgery. In addition, the first patient selected was observed for more than a year before operation was finally decided on and performed in September, 1948.

At the same time that we were engaged with this problem several teams in America were similarly occupied. With some workers the approach has been indirect: Bland and Sweet (1949) have devised and practised a venous-shunt operation in which an anastomosis is made between the azygos vein and a branch of the inferior pulmonary vein, with the intention of relieving the high pressure in the pulmonary circulation. D'Allaines and his colleagues (1949) have used a similar operation in Paris. Harken, Ellis, Ware, and Norman (1948, 1950) have used both direct and indirect septal defect in two patients, and operation upon the mitral valve itself in two patients with one death. Smithy (1949), before his untimely death, operated directly upon the mitral valve in seven patients with two deaths. Murray (1949), of Toronto, mentions two patients in whom he has resected one cusp of a stenosed mitral valve and inserted a section of cephalic vein to function as a new valve.

The largest number of operations upon the valvular stenosis itself have been done in Philadelphia by Bailey, Glover, and O'Neill, who have developed a technique similar to the one we have used. Up to February, 1949 (Bailey, 1949), they had operated upon 10 patients with three successes, but in a later report (Bailey, Glover, and O'Neill, 1950) they mention 22 patients with 11 survivals; when we visited their clinic they had already passed this figure with more successes and a lower mortality.

Selection of Cases for Operation

This is difficult, as substantial reasons on which to base our opinions can come only as more patients are operated on. From many patients with mitral stenosis only a few have been selected as suitable for valvulotomy; in this we have been conservative and have waited until it is clear that the patient is deteriorating and that prognosis without operation is bad. The decision to operate earlier, before changes are so far advanced, and a widening of the field of indications, will depend on the results of surgery, and so far they are encouraging. The possibility of surgery should, we think, be remembered so that the right type of case may be helped at the right time.

The therapeutic problem presented by mitral stenosis involves many more features than the narrowed valvular orifice. Treatment must be considered in relation to the natural history of the disease; the liability of rheumatic carditis to recur or to smoulder; the involvement of the other valves; the usual coexistence of some slight or gross degree of incompetence of the valve; calcification of the valve; the development of pulmonary hypertension with secondary changes in the pulmonary arteries and the lungs; the onset of auricular fibrillation; and, above all,

the extent to which the damaged myocardium can compensate for the obstructed valve. Most of these are interrelated, and elucidation of their relative importance is likely to be difficult and often incomplete.

The following are some of the factors that need consideration.

1. *Presence of Active Rheumatism.*—This is of first importance, and is naturally a contraindication to operation. Smouldering activity is difficult to detect, as the absence of rheumatic pains, chorea, or obvious ill-health does not rule out the possibility, and in fact it should be suspected in young people whose heart size is steadily increasing. The rheumatic process is commonest in the first two or three decades and tends to burn itself out, so that there is less danger of experiencing this in the third decade and after. It is not only the risk of active carditis that has to be excluded but the chance in the younger patient of active carditis recurring spontaneously or even as a result of operation. For this reason patients over 25 or 30 are more likely to be suitable and those under 17 should at present be excluded.

2. *Involvement of Other Valves.*—This means particularly the aortic valves. Though free aortic regurgitation is at present regarded as a contraindication, many cases of mitral stenosis have some minimal involvement of the aortic valve hardly sufficient to cause embarrassment of the heart. A diastolic "whiff" behind the sternum alone would not exclude the patient, as with pulmonary hypertension this may be due to pulmonary incompetence—the Graham Steell murmur. Up to now we have rejected as unsuitable for surgery all cases with an associated aortic valvular lesion.

3. *Mitral Regurgitation.*—This is without doubt a factor of importance, for a high degree of it is a grave threat to operative success and possibly, at this stage, a contraindication to valvulotomy. We have therefore been suspicious of all cases with a loud systolic murmur in the mitral area. The diagnosis of mitral regurgitation with or without stenosis has fallen out of favour, but should be resumed—this time with greater accuracy. A large left ventricle and increased atrial pulsation in the right oblique with a barium swallow are important signs. Free mitral regurgitation will lead to an increasing size of the left atrium, and the association of aneurysmal dilatation of this chamber with a wide mitral valve has been stressed (Parsonnet, Bernstein, and Martland, 1946). In tight mitral stenosis with minimal regurgitation slight or moderate enlargement of the left atrium and some hypertrophy of the muscle will be the rule. A massive left atrium suggests that failure of this chamber has already occurred, due not only to regurgitation but probably to rheumatic involvement of its muscle, which is suggested by the high incidence of auricular fibrillation; it is another contraindication to valvulotomy.

4. *Calcification of the Mitral Valve.*—Most old mitral valves show calcification, which, in addition to interfering further with valvular function, makes surgery more difficult and more dangerous, especially in relation to the risk of thrombosis and embolism. Calcification should therefore be searched for, but it is not a complete contraindication to operation, as is shown by our Cases 5 and 6.

5. *Pulmonary Hypertension.*—The simplest effect of mitral obstruction is a rise of pressure in the left atrium and in the pulmonary bed. This obstruction to the return of blood from the lungs is followed by a rise of pressure on the arterial side as well; pulmonary hypertension and hypertrophy of the right ventricle follow. As time passes these become extreme, pressures near or even above the systemic arterial pressure being reached. Ultimately, secondary sclerotic changes occur in the pulmonary arterial bed. In the early stages relief of the mitral obstruction should relieve the pulmonary hypertension, and even in the later stages it may reduce the pulmonary blood pressure (see Cases 1 and 4). When severe secondary changes have occurred in the pulmonary blood vessels and parenchyma (Parker and Weiss, 1936; Larrabee, Parker, and Edwards, 1949) relief of the mitral obstruction may help, but it cannot bring about a complete reversal of the lung damage.

On the other hand, early hypertension is a strong indication for operation. The association of a heart of mitral contour, with no great enlargement but with prominent vascular markings, either at the hilum or towards the periphery, suggests the development of pulmonary hypertension. These changes correspond to the clinical course of progressive lung symptoms and signs without congestive failure (see below) and in such cases the possibility of operation should at least be considered.

6. *Onset of Auricular Fibrillation.*—The presence of fibrillation is not so much a contraindication to operation as an indication that the optimum time has passed (see Case 5). If this arrhythmia has been present for any time, thrombus formation within the auricular appendage is likely and will constitute an additional hazard as a source of emboli both at operation and after. If auricular fibrillation has been followed by few symptoms and little congestive failure it may well indicate a relatively sound myocardium, and should not then be a bar to the consideration of mitral valvulotomy.

7. *Secondary Right-sided Heart Failure.*—This may be added to the clinical picture, and, although in the early stages it may strengthen the indication for operation, in the later stages it makes success unlikely and must increase the operative risk to to a degree that may be prohibitive.

8. *State of the Myocardium.*—There are few cases of mitral stenosis in which some of the disability is not due to the mechanical effect of the obstruction and some to the damaged muscle; the relative rôle of these two factors will vary and may be difficult to assess. The importance of a damaged muscle as an inevitable contraindication to operation can be overemphasized; it may indeed be an urgent reason for relieving it from its overwhelming burden of forcing blood through the stenosed valve. The correlation between compensatory muscle force and the existence of an obstruction is no new problem in surgery, and some analogy may be drawn with this problem elsewhere in the body—for example, in the bladder or stomach. The surgeon knows from experience that the success of operation for the relief of an obstruction depends in great part on how early it is done, and that the correct time to operate is as soon as a chronic irreversible obstruction is present but before decompensation threatens.

The Surgical Problem

Before deciding upon tactics it is necessary to settle the strategic plan. In trying to relieve the effects of mitral stenosis by operation we must decide two broad principles. Should we use an indirect method, seeking by some form of shunt operation to relieve the pressure effects of the obstruction; or should we use a direct method, seeking to relieve the valvular obstruction itself? The first policy is really that of symptomatic relief only; it does not cure. The second aims not only at symptomatic relief but also at some degree of cure of the underlying disorder. Our policy has been the direct relief of the valvular obstruction. This does not mean that there is no place for indirect methods in certain types of case—probably those with advanced or permanent hypertensive changes in the pulmonary circulation.

The major strategy having been decided, we must consider the tactical or technical details necessary to solve the surgical problems involved. The two chief ones to be discussed here are the route of approach to the mitral valve and the method of dealing with the valvular stenosis.

Route of Approach to the Mitral Valve

The mitral valve may be approached either through the cavity of the left ventricle or across the left atrium, in which case the auricular appendage is convenient. The auricular approach is the method of choice. Cutler and Beck used the left ventricular route, as also did Pribram (1926) and more recently Smithy (1949). It has several grave disadvantages. The approach for adequate exposure

has to be more extensive, and the necessary manipulations may involve much dislocation of the position of the heart, which is liable to be followed by arrhythmias or cardiac arrest—a well-known fact of which we have personal experience in operations through the right ventricle for pulmonary stenosis. The thick muscle wall of the ventricle has to suffer the insertion of stay sutures and then incision, and is further interfered with by the passage of instruments into its interior; bleeding is more likely to be severe. The identification of the mitral valve is more difficult and uncertain from the ventricular aspect, and the chordae tendineae form a closely set obstruction to the approach to the narrow mouth of the valve. This is clearly shown in the latest paper by Smithy, Boone, and Stallworth (1950). It is also difficult to relieve the valvular obstruction efficiently from this aspect, as will be shown in the next section.

In contrast, the atrial route is much simpler. The operative exposure is easy and well tolerated and no dislocation of the heart is involved. This route was first suggested by Allen and Graham (1922). Allen and Barker (1926) showed by electrocardiographic studies on dogs that the ventricular approach caused ventricular arrhythmias, including fibrillation and even cardiac arrest; but cutting, clamping, or suturing the auricular appendage or section of the mitral valve produced little or no disturbance. Although Smithy (1948) and others have shown that the ill-effects of direct disturbance of the ventricular muscle can be lessened by the use of procaine solution, the ventricular route involves greater disturbance to the heart and has other inherent disadvantages. Our own operative experiences impress us that the heart is very tolerant of the auricular approach.

Allen and Graham introduced a cardioscope with an attached cutting knife through the left auricular appendage; it remained for Souttar (1925) to report a case in which the introduction of a finger was used with success. His use of the finger as the basic instrument is a contribution of fundamental importance and forms the basis of what would seem to be the safest and most practicable procedure in use to-day; for this he deserves full credit.

The approach to the mitral valve from its atrial surface is undoubtedly more natural than from its ventricular surface; the finger, once within the atrium, rapidly finds the mitral orifice; its shape, the consistency of its edges and of the valve cusps, and the presence or absence of calcification can all be noted; it is almost as if one sees with the finger. In addition, the presence and degree of mitral regurgitation may be detected as soon as the finger approaches the valve. The finger can then be used, or can carry the instrument, to relieve the valvular stenosis. Equally important is the fact that by this approach alone can the actual relief of the stenosis be done in the most mechanically efficient manner.

Relief of Valvular Stenosis

It is often assumed that relief of a valvular obstruction causes regurgitation. It is, of course, true that severe regurgitation can be caused in this way and can seriously aggravate the condition and even prove fatal. It is not an inevitable accompaniment if the valve is divided properly; indeed, we think the regurgitation may even become less. For instance, if the mitral orifice is a small rigid hole in the middle of a firm diaphragm with free regurgitation, a transverse incision in the correct plane replaces the rigid diaphragm by two more mobile flaps that can certainly function no less and possibly more efficiently.

Cutler and Beck, and more recently Smithy, Boone, and Stallworth (1950), excised or attempted to excise a round piece of the edge of the valve with a cardio-valvulotome. This enlarges the mitral orifice only slightly and causes regurgitation. It is a procedure that should not be used. Consideration of the normal anatomy of the mitral valve and the secondary changes caused by rheumatic valvulitis reveals the proper method of correction of the stenosis.

The mitral valve consists of a larger antero-medial flap and a smaller postero-lateral one; the axis of the valve is not transverse but is directed obliquely forwards and to the left (Fig. 1). As a result of the rheumatic infection

FIG. 1. FIG. 2. FIG. 3.

FIG. 1.—Showing the formation and disposition of the normal mitral valve. Note the oblique direction of the orifice and that the antero-medial cusp is much larger than the postero-lateral one.

FIG. 2.—Stenosis of the mitral valve; the classical buttonhole is surrounded by a zone of thick fibrous tissue. The two cusps are fused so as to form a medial and a lateral commissure.

FIG. 3.—Although exuberant calcification on the medial part of the valve orifice has resulted in a small rigid opening, the basic oval structure with two commissures is apparent.

the valve edges become thickened, deformed, and adherent, and the orifice becomes contracted owing to the partial fusion of the cusps, which themselves suffer a varying degree of thickening and fibrosis. In its simplest form the stenosed orifice is a narrow oval, the classical "buttonhole" stenosis; the axis of the orifice corresponds to that of the original valve (Fig. 2). Even in the severest forms, including those with calcification, this basic pattern exists, but it may not be apparent owing to the orifice being rounded, irregular, or triangular (Fig. 3).

In the severer forms the two valve cusps are thickened throughout and the contracture affects the whole mitral ring, which is smaller than normal; the greatest thickening occurs around the edges of the valve orifice. Sometimes there is partial fusion between the cusps across the opening, so that two, three, or more small apertures are seen. The mitral ring is not always much reduced in size: the valve cusps may be only slightly thickened and still retain much of their pliability, and the fibrous thickening and rigidity is almost entirely confined to the edges of the stenosed orifice. In Case 5, although the medial half of the orifice was calcified, the valve cusps immediately outside the fibro-calcareous margin were thin and supple.

These considerations show that the obstruction should be corrected by enlarging the orifice along the line of the original stoma—that is, antero-laterally and postero-medially (Fig. 4); the original structure of the valve is thus reconstituted and two functioning flaps are provided. Such a manœuvre, far from interfering with the efficiency of the valve and allowing regurgitation, is more likely to make the valve more efficient, since the freed portions of the cusps are larger and more mobile, especially if the cusps are thin and still supple. Even if the valve has a small rigid orifice (Fig. 3) which cannot close in ventricular systole, releasing the cusps enables them to come together.

At the same time that we were forming our own plans on the correct anatomical method to use, Harken and his

colleagues and Bailey and his colleagues had come to essentially similar conclusions. The portions of the fused valve on each side of the oval orifice have been termed the "commissures of the valve" by Bailey, and the operation of their division "commissurotomy."

The actual method to be used in enlarging the orifice along the lines of the commissures is a matter of technical expediency, provided that it does not involve punching out a circular portion of the valve, which would inevitably lead to severe regurgitation (Fig. 5). The enlargement can often

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 4.—Illustrating that the only correct way to incise or split the stenosed valve is along the line of the lateral and medial commissures; in this way the original structure of the valve is, in some part, reproduced. Far from regurgitation being caused or aggravated, the valve cusps are probably more efficient, since some of their mobility is restored.

FIG. 5.—If circular portions of the valve are removed, even at the site of the commissures, regurgitation will certainly follow.

FIG. 6.—A thin sliver can be excised along the line of the commissures and may confer even greater valvular mobility and efficiency.

be made by splitting along the line of the commissures with the finger; or by cutting along this line with a suitable knife or guillotine; or by punching out a thin sliver of the commissures (Fig. 6), which might favour greater mobility of the flaps.

Harken *et al.* (1948) have used a curved cardio-valvulotome designed to punch out a wedge-shaped portion at the commissures; the instrument used is, however, small, and is passed blindly through the auricular appendage in an attempt to engage the mitral orifice by blind manipulation. Bailey and his colleagues have used various forms of knife and guillotine adapted to the curve of the index finger, and have evolved an instrument of considerable efficiency; earlier they used only the finger, following Souttar's technique, but later they have cut the valve along one or both commissures with their own valvulotome.

We also have designed a flat knife, thin and adapted to the curve of the index finger, that can be introduced into the atrium with the finger. We have found it necessary to use this in two cases only; in all the others it was possible to split the valve along the line of the commissure by using the finger.

It is not entirely accurate to describe this manœuvre as "dilatation" of the valve, which implies that the orifice is merely stretched. The valve is split, and in most cases the split is begun and continued with considerable accuracy and can be prolonged until the palpating finger detects that the circular fibres of the mitral ring itself have been reached. The chief disadvantage of using the finger alone is the difficulty of splitting the medial commissure, although this is not always necessary. One must have a suitable knife or guillotine that can be passed in with the finger to divide the thickened margin of the stenosed orifice quickly and efficiently if the least difficulty is experienced in splitting with the finger.

The antero-medial cusp of the mitral valve is larger than the postero-lateral cusp; it is also called the "aortic" cusp, and this will remind us that it exercises an important function in directing the blood in systole away from the atrio-ventricular orifice and towards the aortic orifice; in fact, it may well be regarded as a functional part of the approach to the aorta.

Harken and his colleagues have shown that damage of this cusp is much more harmful than that of the postero-lateral one. An incision across it (at right-angles to the axis of the valvular orifice or to the line of the commissures) inevitably produces severe acute mitral regurgitation and in the experimental animal is apt to prove rapidly fatal. They thought that twice as many animals died from destruction of the anterior cusp as from a corresponding destruction of the posterior cusp. They also showed that when an anterior defect was produced the rise in pressure in the left atrium from regurgitation was roughly twice as high as after production of a posterior defect. It is therefore quite certain that the integrity of the antero-medial aortic cusp must be preserved and that it must neither be cut into nor injured by punching with a cardio-valvulotome.

The Operation

In all cases anterior thoracotomy was done through the third left interspace with division of the third or fourth or both costal cartilages. Intravenous procaine was at first given only as occasion arose, but we now use it as a routine. Procaine solution 4% is instilled into the pericardium and left for at least five minutes before the pericardium is opened; swabs soaked in the same solution are then applied to the base of the auricular appendage. We have not injected procaine solution into the wall of the atrium, and have so far observed no disturbance when a clamp is applied to the base of the auricle or when the finger is introduced into the atrial cavity. When the mitral orifice itself is obstructed by the finger, which is never for more than two or three heart beats, there is, of course, disturbance of the heart's action, but this is corrected as soon as the finger is removed from the orifice.

A curved clamp is placed across the base of the auricular appendage and two opposing purse-string sutures are then inserted immediately distal to it. The auricular appendage is incised along one side, leaving it attached medially; the end of the appendage is not amputated at once, as it is felt that it might prove useful to seize if the appendage should slip away during later manipulations. Any cross bands are divided so that the auricular cavity is completely freed; any clot is of course removed. When an adequate orifice has been obtained the index finger is slid forwards into the atrial cavity as the clamp is loosened; in this way no haemorrhage should occur. If the fit is not snug enough the purse-string sutures can be slightly tightened. After the valve has been split or cut, the finger is withdrawn and the clamp simultaneously reapplied. The tip of the auricular appendage is removed and the opening closed by interrupted sutures and reinforced by tying the two purse-string sutures. The operative findings in Case 1 are important and may be taken as representative.

The pulmonary artery was found to be very large—much larger than the aorta of an adult man. The index finger was easily introduced into the left atrium, but on this, the first occasion on which we had performed this manœuvre, the state of affairs within the heart was very different from what was expected from post-mortem observation. The chief impression gained was of the powerfully contracting left ventricle; instead of the lower part of the atrial cavity forming a funnel leading to the mitral orifice, this part was found to be almost flat in diastole, and in systole it became convex towards the finger like a sail in the wind; the whole base of the heart rose towards the finger in

systole. Actually the mitral orifice was located at once, but was so much smaller than expected that it was not appreciated at first that the orifice was certainly that of the mitral valve; one anxiety was that it was the opening of a pulmonary vein.

The mitral orifice just admitted part of the tip of the finger and measured about 0.75 by 0.25 cm.; the mitral ring itself seemed to be little more than 2.5 cm. in diameter; the cusps were not very rigid. There was no difficulty in splitting the opening laterally and medially along the line of the commissures until the whole index finger passed readily into the left ventricle as far as the apex; the splitting and enlargement of the valve was not done in one movement but with a series of pauses during which the finger was withdrawn from the valve orifice so that the circulation was not obstructed for more than two or three beats at a time. Moreover, it was felt that it was better not to enlarge the orifice too rapidly, but to allow the circulation time to accommodate to the relief of the obstruction.

The diameter of the surgeon's index finger at the proximal interphalangeal joint is just over 2 cm., and the valve orifice was now so near the mitral ring that it was thought to be unnecessary and unwise to incise the commissures. The finger was within the atrium for about 10 minutes—a much longer time than in any subsequent operation when familiarity with the local conditions had been gained. Whereas when first exposed the atrium was very tense, at the end of the valvulotomy the pressure within it was obviously very much lower. The heart's action was undisturbed by the manipulations except when the mitral orifice was completely blocked; the heart then reacted violently and the blood pressure fell towards zero, but recovery occurred as soon as the finger was removed from the valve.

We have not taken records of intra-atrial pressures before and after valvulotomy, because we wished to do nothing that was not strictly therapeutic in these earlier operations, when we were trying to assess what the heart could tolerate. In addition, with the chest open and many other factors causing a drop in pressures, the changes observed might not give an accurate picture.

Cardiotomy and relief of valvular stenosis has been done in eight patients; in two of these a cutting valvulotome was used, but in the others the valve was split with the finger. The actual operation was well tolerated by all. Two patients died—one on the day after operation, and the other four days after, following a haemorrhage complicating heparin therapy, which was unwisely begun 24 hours after operation because of a cerebral embolus; we believe that without the heparin she would not have lost her life. One other patient suffered a cerebral embolus (Case 1), but made a complete recovery.

Notes of the eight cases follow. To save space some details that are given in Tables I and II are not repeated in the text. The clinical picture has been given in more detail so that the reader can judge the type of case operated upon and the degree of improvement.

Case 1

Pulmonary symptoms for seven years and recurrent pulmonary oedema for three years; complete incapacity; normal rhythm. Good result of operation maintained for 20 months; able to walk three miles (4.8 km.) instead of 100 yards (90 metres).

This patient was 23 years old when seen in October, 1947. Dyspnoea was first noticed when she was 17 and working as a land girl; it increased steadily over the next six years. There was no history of congestive failure, but in the previous two years she had been admitted to her local hospital with attacks of "pneumonia." She was referred to us by Dr. E. D. Y. Grasby, of Pembury County Hospital.

The physical signs indicated mitral stenosis (see Table I). There were moist sounds at both bases, but no enlargement of the liver or systemic oedema. Cardiac catheterization showed an increase of pressure in the right ventricle and pulmonary artery (see Table II). Though it was thought that pulmonary oedema was probably the cause of such frequent attacks, an infective element could not be excluded, and it was decided to watch her to make sure she could not be improved by medical treatment.

During the next eight months her dyspnoea increased, and she had further attacks of "pneumonia" and lost another 13 lb. (5.9 kg.) in weight (to 89 lb.—40.4 kg.). She was not able to walk more than 100 yards (90 metres). She was never well enough to get up to the out-patient department, and when she finally came by ambulance in July, 1948, she was very much worse and was at once admitted to hospital.

She was breathless walking about the ward. She had a malar flush and cyanosis of the lips after exertion, but no congestive failure. At the apex there was a diastolic murmur typical of mitral stenosis, but no systolic; at the third left interspace a blowing systolic and diastolic murmur, thought to be evidence of pulmonary rather than aortic regurgitation, had appeared since she was last seen; the pulmonary second sound was loud and reduplicated.

Crepitations were heard all over the lungs, not confined to the bases as before. The heart had increased in size with blurred outlines; the vascular markings throughout the lung fields were more prominent than those usually seen in simple congestion. Both pulmonary branches were greatly dilated as in cases of

TABLE I.—*Clinical Data of Patients with Mitral Stenosis Submitted to Mitral Valvulotomy*

Case No.	Sex and Age	Duration of Dyspnoea	Duration of Pulmonary Oedema	Haemoptysis	Duration of Congestive Failure	Duration of Auricular Fibrillation	Apical Systolic Murmur*	Blood Pressure	Cardio-thoracic ratio
1	F 22	6 yrs.	3 yrs.	−	No	No	No	120/85	56%
2	F 36	10 ,,	Yes†	+	No	5 yrs.	No	110/70	60%
3	F 39	8 ,,	No	−	3 yrs.	3 ,,	Yes	115/75	68%
4	F 36	8 ,,	8 yrs.	+	1 yr.	1 yr.	Yes	100/70	64%
5	M 42	3 ,,	6 mths.	+	6 mths.	6 mths.	No	120/80	68%
6	M 31	2 ,,	Yes	+	No	3 ,,	Yes	102/74	51%
7	F 23	4 ,,	6 mths.	+	No	No	No	107/70	—
8	M 26	4 ,,	No	+	No	No	No	100/70	—

* All cases showed typical diastolic murmurs of mitral stenosis; all had accentuation of the pulmonary second sound. All had marked right axis deviation.
† Only when pregnant seven years previously.

TABLE II.—*Data Obtained by Cardiac Catheterization in Patients with Mitral Stenosis. Before and After Operation. The Figures in Parentheses Indicate the Results After Operation*

	Case 1*	Case 2	Case 3	Case 4*	Case 5*	Case 6	Case 8
Pressure in mm. Hg R.A.	16† (8)	10	11	7 (0)	12 (12)	3	12/0
Pressure in mm. Hg R.V.	68+ (23)	18	40	55/10 (35/0)	36 (65/13)	67/2	
Pressure in mm. Hg P.A.	68+ (40)	20·5‡	78	63/26 (35/10)	59 (70/30)	73/50§ (41/20)	130/78
Oxygen percentage—arterial	90·5 (96)	91	95	95 (94)	95 (95)	93·4	91
Oxygen saturation—mixed venous blood	45·5 (64)	43	49	54 (64)	53 (64)		44·7
Cardiac output in litres a minute	2·6 (3·3)	2·4	3·0	2·5 (3·3)	2·9 (2·7)	2·1‖ (2·3)	2·71¶

* Pre-operative figures 9 to 12 months before operation. † Reading may be too high owing to possible clotting in catheters. ‡ Pulmonary capillary pressure. § Rose to 100/78 on exercise. ‖ Rose to 2·6 on exercise. ¶ After exercise, 2·65.

atrial septal defect, but without pulsation. The right ventricle and left atrium were moderately enlarged in the oblique views.

Valvulotomy, September 16, 1948. Anaesthetist, Dr. Hutton. Thiopentone and curare with intratracheal cyclopropane and ether. Blood transfusion, 450 ml.

The findings inside the heart at operation in this case have already been detailed in the general description of the operation (see above). The general condition at the end of operation was good and the blood pressure was 95 mm. This continued for 48 hours, when she became drowsy with bilateral extensor plantar responses and a right-sided hemiplegia. Sir Charles Symonds diagnosed a succession of emboli to both middle cerebrals. A heparin drip was given for the succeeding eight days; there was no further extension and her hemiplegia gradually improved.

Her cardiac condition was remarkably good, the lungs remained dry, her pulse was steady at 80 by the fourth day, and her blood-pressure level gave no anxiety. For the first few days after operation no diastolic murmur at the apex was heard, though there was a roughish systolic murmur, but as her condition improved and her activity increased a low rumbling diastolic appeared. Her progress was steady and she was allowed to increase her exercise gradually until after five weeks she went up and down two flights of stairs without distress. Cardiac catheterization eight weeks after operation showed improvement. Mean pressures (measured from the skin of the back) and oxygen saturation figures are given in Table II. As will be seen, the cardiac output increased from 2.6 to 3.3 litres a minute.

The pre-operative pressures were probably much higher than those just before operation, as they were obtained almost a year before operation, when her condition had been much better.

The patient's subsequent course has been very encouraging. Two weeks after discharge from hospital she could walk half a mile (0.8 km.) slowly, climb stairs, and help in the house—which she estimated as equal to her capacity three or four years before operation. Six weeks after discharge she had walked a mile (1.6 km.) without symptoms, she had no cough, and was 7 lb. (3.2 kg.) heavier; the diastolic murmur was obvious, and the lung bases were clear.

Twenty months after operation she walked three miles (4.8 km.), her weight has increased by 14 lb. (6.4 kg.) and she is leading a normal quiet life at home.

Case 2

Severe disability with recurrent haemoptyses without right-sided congestive failure or gross enlargement. Successful valvulotomy, but cerebral embolism. Death from bleeding after heparin.

A married woman aged 36 was able to play some games at school, and later tennis, but was breathless compared with her friends. When she was 21 she began to notice breathlessness in her ordinary life, and at 26 she became much worse and had to be in bed for several months. When the war came she was able to work as an ambulance driver for a year.

In June, 1941, when she was 29 and was six months pregnant, she complained of severe nocturnal dyspnoea and coughed up some blood-stained sputum. Caesarean section and sterilization were performed in October, 1941.

From 1942 to 1945 she was worse and haemoptysis was frequent, lasting on and off for eight weeks in 1943, and returning two or three times a year. When seen in 1948, at the age of 36, she was very incapacitated and could hardly do any shopping or housework. She could walk only 200 yards (183 metres) and also complained of a tight feeling in the mid-sternum on walking, which was sometimes quite severe. The heart was a little larger—c.t.r. 60 (15/20 cm.); this being due to the right ventricle and left atrium. There was a long diastolic murmur and thrill and the diastolic murmur was heard up to the pulmonary area. Moist sounds could be heard in both lungs. The liver was not felt, and oedema of the ankles was not present. There was auricular fibrillation, but it was not easy to be sure when this had started—perhaps five years before.

Cardiac catheterization showed little if any increase of pressure in the right ventricle or pulmonary artery (see Table II).

Mitral valvulotomy, September 28, 1948. Anaesthetist, Dr. E. H. Rink. Thiopentone and curare, cyclopropane, and ether.

The pulmonary artery was large, prominent, and tense; the auricular appendage was large and was occupied by a thrombus from which an indurated area about 2.5 cm. in diameter extended on to the lateral wall of the atrium; a slight yellowish discoloration could be seen over it. A clamp was applied to the base of the appendage, which on being opened disclosed yellow organized clot. A finger was inserted, but the way seemed to be completely blocked; it was withdrawn, and inspection showed it had been inserted between the myocardium and the clot. It was now inserted medial to the clot, and entered the atrium and passed down to the valve at once. The opening in the valve was very small, no more than 0.75 by 0.4 cm.; an adhesion could also be felt as a strand across the orifice. The orifice was slowly and steadily split with the finger, both laterally and medially, until the finger passed through as far as the proximal joint. The edges of the opening were now so rigid that further splitting was not possible; the finger was withdrawn and reinserted carrying a valvulotome, with which an incision was made in the lateral commissure. The orifice was much enlarged by this and the finger could be moved freely about; the orifice seemed to be about 2.5 by 2 cm. The intracardiac manipulations lasted seven minutes and were well tolerated except for the usual reaction when the orifice was completely blocked.

The patient's general condition on return to bed was satisfactory. Later it became clear that cerebral embolism had occurred, no doubt from the disturbance of the clot in the auricular appendage. On the following day she was still drowsy but could speak; she had a left-sided facial paralysis, weakness of left conjugate deviation, paralysis in the left half of the tongue, and some choking on swallowing water; she moved the left arm and elbow but not the left wrist or hand; movements of the left lower limbs were diminished. Sir Charles Symonds diagnosed an embolism of a branch of the middle cerebral artery. After much discussion heparin was given by intravenous drip 24 hours after operation. Her general condition was satisfactory apart from the embolus; the pulse rate was 90.

The decision to give heparin proved unfortunate, because the next morning a large effusion was found in the left chest; 2.5 litres of fluid blood was removed, and it was clear that massive oozing had occurred. In spite of blood transfusion and other treatment she did not rally, and died four days after operation. If heparin had not been given we think she would not have lost her life.

Necropsy showed infarction in the right cerebral hemisphere. The operation site in the heart was satisfactory; the mitral orifice easily admitted the whole length of the index finger, and its edges were clean and smooth, with the exception of a thin fibrin deposit on the lateral commissure where the incision in the valve had been made. The medial commissure was very short, less than 1 cm., and it would not have been possible to enlarge the orifice much further in that direction.

Case 3

Auricular fibrillation with attacks of congestive failure for three years; pulmonary hypertension, but lung symptoms not prominent; loud apical systolic murmur suggesting mitral regurgitation; death 36 hours after operation.

A housewife aged 39, without children, had had dyspnoea for the past eight years, but she worked until the last three years, when this symptom increased suddenly with the onset of auricular fibrillation. After rest in bed and treatment with digitalis she resumed her housework and shopping, but movement was very limited through dyspnoea and oedema of the ankles, and she slept propped up at night. She gave no history of haemoptysis. She lost 14 lb. (6.4 kg.) in weight during these three years.

On admission she was thin and asthenic. Her complexion was sallow, with a malar flush; she had poor peripheral circulation, with cold extremities and a faint cyanotic tinge. The neck veins were prominent even when she was sitting. The liver was slightly enlarged and oedema of the feet could be elicited by prolonged heavy pressure. There was slow fibrillation. There was a Grade 3 blowing systolic murmur, maximal at the apex but heard over a circle 7.5 cm. in radius. Air entry was good, with no adventitious sounds at the bases. Cardioscopy showed a very large heart (15/22 cm.) due to the right ventricle, the left ventricle being of normal size; the left atrium was moderately enlarged. Calcification of the mitral valve was not seen. (See Tables I and II for physical signs and results of catheterization.)

Valvulotomy, January 17, 1949. Anaesthetist, Dr. E. H. Rink. Thiopentone and curare followed by cyclopropane and ether. Blood transfusion of 600 ml.

The pulmonary artery was as large as a normal aorta and under high tension; the left auricular appendage was large and prominent and also under high tension. During all intracardiac manipulations the left common carotid artery was compressed by the anaesthetist to lessen the chance of cerebral embolism. The mitral valve orifice was easily found; it was about 1 by 0.75 cm., and its margins were heavily calcified. The lateral commissure was slowly and progressively split quite easily until the mitral ring was reached; the medial commissure was not split. The index finger readily passed through the enlarged orifice. The finger was within the heart for about 10 minutes; the whole manœuvre was well tolerated and the heart showed no disturbance. The pressure in the left atrium was obviously reduced.

The post-operative course for the first 12 hours was encouraging, but the blood pressure failed to rise above 90/60 despite methedrine and intravenous fluids. Twenty-four hours after operation 15 oz. (425 ml.) of blood was aspirated from the left chest. The patient was conscious, but her blood pressure gradually fell and, despite a rate generally under 100, her pulse became feebler until she lost consciousness and died 36 hours after operation.

At necropsy the myocardium showed no gross evidence of disease. There was a moderate degree of tricuspid stenosis and a large atrium. Ante-mortem thrombus filled the left auricular appendage and extended as a thin strand on the divided lateral commissure of the mitral valve. The anterior cusp of the mitral valve revealed pronounced calcification extending on to the chordae tendineae and the atrial surface. The lungs showed typical brown induration, but were not oedematous, infected, or infarcted. The liver was enlarged, tawny, and cirrhotic, and there was a scar from an old infarct in the right kidney.

Case 4

Severe mitral stenosis with seven years of increasing pulmonary symptoms, including repeated cardiac asthma, and one year of right-sided failure and auricular fibrillation; completely incapacitated. Successful operation with no complications. Able to work and walk two miles (3 km.).

A nursery governess aged 35 was a children's nurse until the age of 23, when she found difficulty in doing a full day's work. When 27, breathlessness on exertion increased and she had her first attack of cardiac asthma. After three months' rest she worked for the next three years, but was more breathless on exertion. Her second attack of cardiac asthma occurred when she was 32 and she was admitted to hospital; this happened on five subsequent occasions for periods up to seven weeks in different parts of the country where she was employed. In the earlier admissions there seems to have been no right-sided failure, but in the summer of 1948 she was admitted with congestive failure. She then had auricular fibrillation, but the time of onset of this is not known, though digitalis had been taken intermittently over the previous three years. She was admitted to Guy's in February, 1949, having been seen at the National Heart Hospital by Dr. Paul Wood, who thought that operation on her mitral valve should be considered.

On admission, she was small and slightly built. She was orthopnoeic, but showed no venous congestion or oedema. There was cyanosis in lips, ears, and extremities. She became breathless after walking 10 yards (9 metres). She had auricular fibrillation. Radiologically the heart showed enlargement of typical mitral conformation, measuring 16/25 cm.; the left atrium was enlarged.

She improved while in hospital and was discharged; she was given mersalyl injections and digitalis to see if this improvement might be maintained without operation. She was, however, clearly unfit to resume her work as a nursery governess, or even to do any light work. She was most anxious that operation should be attempted, as she had no home and no one to look after her.

Valvulotomy, June 30, 1949. Anaesthetist, Dr. Carnegie. Thiopentone and intratracheal nitrous oxide, oxygen and ether. Intravenous saline, 600 ml.

The pulmonary artery was the usual huge tense structure; the pulmonary veins were also large and tense, as also was the left atrium; the auricular appendage was small and barely large enough to be used with safety.

The stenosed mitral orifice was located as soon as the finger entered the heart; it was rather less than 1 by 0.5 cm. and the valve cusps were surprisingly thin; the only obvious induration was around the edge of the orifice; there was no calcification. It was a simple matter to split both commissures across with the finger as far as the mitral ring. The new orifice was much larger than one finger; the mitral ring seemed to be of normal size. At the end of the operation the general condition was satisfactory and her colour was much better. She made a good and rapid recovery.

In late September, 1949, she was readmitted for cardiac catheterization. She had been able to push a perambulator with two children for two miles (3 km.) without distress. She had gained 7 lb. (3 kg.) in weight. There had been no oedema of the ankles, but she still slept with three pillows. She still had auricular fibrillation. There was a soft systolic and a doubtful mid-diastolic murmur at the apex; the pulmonary second sound was still increased. The heart was slightly decreased in size 14.5/25 cm., and the pulmonary conus looked slightly less prominent. Cardiac catheterization gave the following information, the pre-operative findings being given in parentheses.

	Right Atrium	Right Ventricle	Pulmonary Artery
Percentage oxygen saturation	65 (80)	64 (84)	64 (84)
Pressure in mm. Hg ..	0 (7)	35–0 (85–10)	35–10 (83–26)

Cardiac output, 3·3 litres per minute (2·5)

There was therefore a significant decrease in the pressures in the right ventricle and the pulmonary artery, and 0.8 litre a minute more blood was passing through the mitral valve at rest.

She left hospital and her condition was satisfactory enough to approve of her taking a position as a "nanny" to travel to South Africa and back. After eight months she was doing a full day's work without distress and was able to push a baby in a perambulator three miles (4.8 km.). There had been no return of cardiac asthma, and she had successfully surmounted a heavy winter cold.

Case 5

Late onset of symptoms of pure mitral stenosis, but rapid progress of lung symptoms and signs over three years; right-sided failure with onset of auricular fibrillation; successful operation with temporary return to normal rhythm; much improvement with return to full working day.

A man aged 41 was first seen in April, 1948. The first evidence of mitral stenosis was a large haemoptysis 18 months before, though he had been slightly breathless for six months. He changed from heavy to clerical work, but was troubled by increasing dyspnoea and cough. The rhythm was normal and the heart small for the degree of disability.

He was admitted to Guy's in September, 1948. He was a well-built athletic type of man. There was no cyanosis nor any evidence of venous engorgement nor oedema. His heart was slightly enlarged, with a prominent pulmonary conus and main branches, and a granular mottling of the lung fields; the right ventricle and left atrium were moderately enlarged. He was still able to earn his living as a clerk, being conveyed to and from his office in a friend's car; but in April, 1949, with the onset of auricular fibrillation his dyspnoea suddenly increased, there was more orthopnoea and oedema of the ankles, and his heart had increased in size from 17 cm. to 19/29 cm. He was admitted to hospital, where his congestive failure was relieved and his heart decreased in size (17.5/28.5 cm.); but a month after admission he had his first attack of cardiac asthma and an embolism involving one toe. He attempted to return to work, but it was beyond him, and in one month he had four more attacks of cardiac asthma and could sleep only sitting up. It was decided to operate before further deterioration occurred.

FIG. 7.—Showing valvulotomy performed along the line of the lateral commissure in Case 5, in which the medial commissure was calcified.

Valvulotomy, September 5, 1949. Anaesthetist, Dr. Carnegie. Thiopentone and curare, cyclopropane and ether. Intravenous saline, 1,200 ml. The general condition was very unsatisfactory during induction of anaesthesia, with rapid and irregular pulse rate as high as 180, which was slowed to 140 by the use of intravenous procaine solution.

The pulmonary artery was the usual huge tense structure. A large long appendix projected from the tense left atrium. The finger was introduced without difficulty and at once a powerful jet of regurgitant blood could be felt with each ventricular systole; this was noteworthy, as no systolic murmur had ever been heard. The mitral orifice (Fig. 7) was grossly calcified around its medial two-thirds in front, medially, and behind. Lateral to this calcification was a small rigid triangular orifice through which the blood could be felt to regurgitate. The edge of this part of the opening was slightly thickened, but the valve cusps were thin and the lateral commissure was easily split open as far as the mitral ring. Although regurgitant blood could still be felt it seemed less and the jet had lost its power. The most dramatic event was an immediate slowing of the heart, which was also felt to become more regular. Almost at once Dr. Reynolds, who had been taking electrocardiographic tracings, reported that auricular fibrillation had ceased. By the time the auricular appendage had been closed there was slight dissociation between the ventricular and atrial rates, which were about 120 and 110 (Fig. 8). A few minutes later Dr. Reynolds reported that normal sinus rhythm was established (Fig. 8).

The patient's general condition at the end of the operation was much better than at the start, and he had a good colour; his pulse was 120 and regular.

The return to normal rhythm within one minute of the relief of the obstruction (Fig. 8) was most dramatic. His post-operative course was remarkably smooth. The pulse rate was steady at 90 with sinus rhythm, and the blood pressure showed no tendency to fall. On the second day there were frequent auricular extrasystoles and on the third day auricular fibrillation returned. An apical systolic murmur had appeared at the apex, and for the first week no diastolic murmur was heard, though it returned later. He was up in two weeks, and six weeks after operation his heart was again catheterized. The findings are summarized in Table II (with the pre-operative findings of one year before in parentheses).

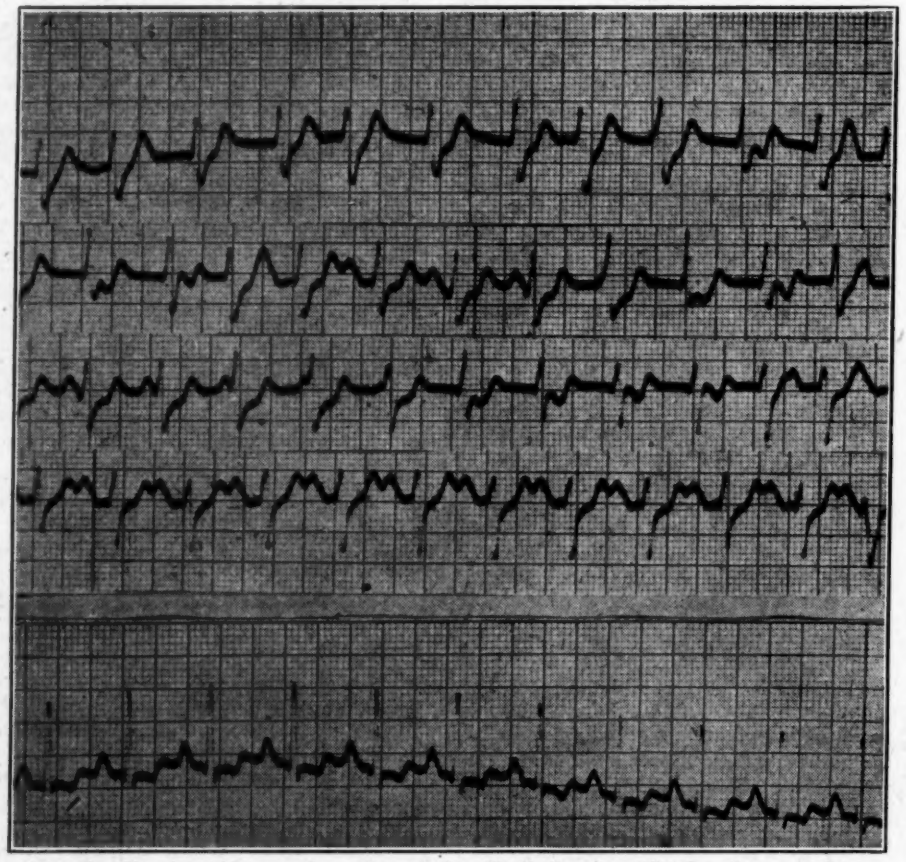

FIG. 8.—Showing the cessation of auricular fibrillation immediately after valvulotomy (Case 5). The upper curve shows auricular fibrillation with P waves appearing towards the end, though probably still with complete dissociation. In the second, third, and fourth curves, which were taken continuously, the P waves are present throughout and regular, but there is probably still complete dissociation until the fifth curve, where the relationship of P to QRS has become regular and there is a consistent response still with tachycardia. In the fifth curve, taken 40 minutes later, the rate is a little slower and the P waves are better separated from the T waves and show normal rhythm.

The cardiac output was 2.7 instead of 2.9 litres a minute. The pressure in the right ventricle and pulmonary artery was not greatly reduced—a disappointing finding in view of his striking clinical improvement.

He was discharged seven weeks after operation, and a fortnight later had walked a mile (1.6 km.) without discomfort, compared with his previous distress on walking about the ward. He was allowed to resume work and has continued since. Six months after operation his condition is satisfactory. He has walked a mile and a half (2.4 km.) without dyspnoea and feels he could do more; he sleeps with only one pillow and has had no further cardiac asthma; his colour is good, there is no oedema, and the lung bases are clear. There is no change in the size or shape of the heart on screening, though perhaps the pulmonary conus is less prominent: the mottled opacities in the lung fields are less marked.

	Right Atrium	Right Ventricle	Pulmonary Artery
Pressure in mm. Hg from skin of back	12 (12)	65–13 (38)	70–30 (59)

Case 6

Progressive dyspnoea and haemoptysis for two years. Auricular fibrillation. Severe pulmonary oedema and incapacity. Successful operation with immediate good result.

A draughtsman aged 31 had chorea and rheumatic fever as a child. He was seen in 1931 by Dr. Helen Taussig, and his heart was then normal. He continued under Dr. Taussig's observation, and it was due to her courtesy and to Dr. Alfred Blalock's that one of us was asked to operate on him and also upon Case 7 at the Johns Hopkins Hospital.

In 1932 he had acute rheumatism again, and after this a systolic murmur developed; in 1935 he had established mitral stenosis. Several more attacks followed, and he entered hospital for the last one in 1937. He continued fairly well for the next ten years and worked as a draughtsman. He was unaware of any marked limitations until about two years ago, when he began to lose ground steadily; he coughed almost all the time and often brought up blood. Dyspnoea on exertion became progressive, and he found it increasingly difficult to get to and from his work, which was a 20-minutes walk. For three months he had noticed occasional bouts of palpitation, which would last for a few hours (presumably auricular fibrillation). He could just manage to walk about the room.

He was admitted to the Johns Hopkins Hospital on October 4, 1949. He was thin and pale, slightly dyspnoeic at rest, and orthopnoeic. Auricular fibrillation was present.

The heart was enlarged, the apex beat being almost in the anterior axillary line in the fifth interspace; a diastolic thrill could be felt at the apex; a rumbling diastolic and a blowing systolic murmur were heard. The liver was not enlarged. Radiography showed a heart of typical mitral appearance, with some enlargement of the left atrium. Calcification of the mitral valve, 1 cm. in thickness, was reported to be present.

In view of his steady deterioration, especially during the previous two months, and his present severe disability which confined him to the room, operation was recommended and eagerly accepted by the patient.

Valvulotomy was carried out on November 17, 1949. He was anaesthetized slowly by Miss Olive Burger with cyclopropane and became rather apprehensive and struggled; thiopentone was then administered and an intratracheal tube was passed. Almost at once acute pulmonary oedema developed and his condition became grave. Venesection, 250 ml., was done, tourniquets were applied to his limbs, and he was given a further dose of atropine and morphine; all this time his bronchi were being sucked clear of oedema fluid. He improved considerably, and by the end of 30 minutes the pulmonary oedema had gone.

The difficult decision now had to be made whether to proceed with operation or not. After some deliberation it was decided to proceed, as it was unlikely he would be much better on a later occasion. Curare was given and anaesthetization proceeded with; before the operation began he had two more episodes of pulmonary oedema, though these were less severe. The pulmonary artery was enormous and under great tension; the left pulmonary veins were also large and tense, as also was the left atrium. The left auricular appendage was large; distortion of its surface and irregular thickening on palpation indicated thrombus formation. Fortunately the clamp could be applied proximal to this clot, as was confirmed when the auricle was opened; much clot was removed, most of it buffy in colour; portions were polypoid, white, and smooth.

When the finger was inserted into the atrium an obvious stream of regurgitant blood could be felt. The mitral orifice was at once located and was a small oval about 1 by 0.5 cm.; the lateral part was lightly calcified in a thin layer on the atrial surface and on the valve rim; this calcification was not enough to contraindicate division of the valve at this site. The valve split easily along the line of the lateral commissure as far as the mitral ring, and the opening was now large enough to admit the finger freely and loosely, being estimated at 3 by 2 cm. The medial commissure was palpated but could not be split with the finger.

His condition was satisfactory at the end of the operation and the lungs seemed quite dry; the blood pressure was 110/80 and the pulse, although irregular, was about 100.

He made a smooth recovery, with immediate improvement in colour and relief of orthopnoea. He left hospital and was able to do much more than before operation.

Case 7

Increasing dyspnoea for four years. Acute pulmonary oedema for six months. Normal rhythm with no general cardiac enlargement. Successful valvulotomy with immediate improvement

This patient, a married woman aged 23, was always active in sports. When she was 18 a routine examination disclosed the presence of mitral stenosis, and soon after this she began to notice slight dyspnoea on exertion. She married at 19, and while on her honeymoon tried to ride a bicycle and for the first time noticed real limitation of her activities from dyspnoea. Since then the dyspnoea steadily increased until she became short of breath on climbing one flight of stairs; she noticed brief, sharp pain occasionally on exertion. She had slept with two pillows for the last three years. During the last six months she had four episodes of typical acute pulmonary oedema with extreme dyspnoea and cough with frothy blobs of sputum; each attack lasted eight to ten hours and ceased suddenly. Two of these attacks were brought on by coitus. She continued working as a stenographer, but had noticed mild oedema of the ankles at the end of the day for the last few years.

She looked well but pale. The pulse was regular. On radiography the heart was not generally enlarged, although the left atrium was moderately enlarged; the pulmonary artery was large and prominent, as also was the infundibular portion of the right ventricle. The lungs showed increased markings suggesting chronic passive congestion.

Cardiac catheterization (Dr. Richard Bing) showed a moderate rise in pressure in the pulmonary artery and right ventricle with a sharp rise of pressure on exercise and a fall in cardiac output.

Because of her recent deterioration with several attacks of acute pulmonary oedema a right-to-left venous-shunt operation had been suggested. Dr. Sanford, however, asked for valvulotomy, and this was agreed to and accepted by the patient.

Valvulotomy, November 26, 1949. Anaesthetist, Miss Olive Burger. The whole procedure went very smoothly; the mitral valve showed the typical contracted oval orifice about 1.5 by 1 cm.; it was split towards both commissures without difficulty, so that the finger passed through freely and easily. Recovery was uneventful and the patient was discharged from hospital in good condition. It is as yet too early for a full progress report.

Case 8

Steady deterioration for nine years; further deterioration during two years of observation. Severe dyspnoea on exercise, 20 yards (18 metres) being the limit in comfort and 150 yards (137 metres) absolute maximum. Severe pulmonary hypertension. Successful operation.

A clerk aged 26 had rheumatic fever at the age of 4 and mitral stenosis was diagnosed in 1938. In 1942 he had a haemoptysis. Radiographs showed very large pulmonary vessels and also scattered markings and calcified areas suggesting haemosiderosis. He led a very restricted life, being unable to run, and could walk only about 20 yards before becoming very breathless; 150 yards was his absolute maximum. The pulse was regular.

Valvulotomy, March 2, 1950. Anaesthetist, Dr. Hutton. Thiopentone, curare, nitrous oxide, and oxygen. The mitral orifice was a small narrow oval measuring about 1 by 0.4 cm.; the whole mitral ring was small, measuring little more than 3 cm. The lateral commissure was split with the finger to within 0.5 cm. of the mitral ring and the division completed with a valvulotome. The medial commissure was split with the finger. The operation was well tolerated.

Auricular fibrillation developed on the third day after operation, but was controlled by digoxin, and recovery was then rapid and uneventful. The operation is too recent for assessment of the final result.

Discussion

In the trial period of all major and potentially dangerous operations it is rarely possible to choose the ideal case. It is unfortunate, but true, that difficult surgery has often to be worked out first on the more advanced cases in which the risk of operation is greater and the chance of a good result smaller. Although our experience is limited it is enough to show that direct operation on the stenosed mitral valve is justifiable and helpful. It should now be recommended in suitable cases before they have deteriorated too far.

Ideally the most suitable case is a young adult with established mitral stenosis, without evidence of recent rheumatic infection or symptoms to indicate that failure is imminent.

We feel that it is wrong to attempt operation on middle-aged patients with gross cardiac enlargement and chronic heart failure. Many of these are beyond hope of relief by valvulotomy, but with greater experience it may prove possible to submit some of them to operation. Case 3, for example, tolerated the operation well, but after a promising first 24 hours forward failure overcame her: the large heart and the presence of a systolic murmur were pre-operative danger signals; some degree of tricuspid stenosis, undiagnosed in life, and cardiac cirrhosis, which should have been suspected, were additional posthumous contraindications.

It will be seen from our cases that the various adverse factors mentioned earlier are not absolute contraindications; some degree of them may have to be accepted; it is the advanced degree of these changes that counts against operative success. Those that need special mention are gross cardiac enlargement, of the right ventricle because it foreshadows failure, or of the left ventricle because it may indicate aortic regurgitation or free mitral regurgitation; aneurysmal dilatation of the left atrium; gross enlargement of the pulmonary artery; gross secondary vascular changes within the lungs shown radiologically; severe pulmonary hypertension observed by catheterization; and continued congestive heart failure. One attack of mild congestive failure is no bar to operation, as is shown by Cases 4 and 5.

In contrast, we prefer the heart that is not much enlarged and without evidence, indirect or direct, of gross pulmonary hypertension. Auricular fibrillation is undesirable, but it is in itself no contraindication, though it increases the risk of intra-auricular thrombosis. In fact, the onset of fibrillation, like the onset of congestive failure, may serve as a stimulus to make the decision in favour of operation.

Attacks of recurrent "bronchitis," cardiac asthma, and pulmonary oedema (Cases 4, 5, 6, and 7), particularly in a case with little increase of heart size, are strong indications for considering operation. This group of "oedematous mitral stenosis" with regular rhythm, without great enlargement of the left atrium, and without oedema of the legs, was clearly defined by Gallavardin (1921, 1934), and it is this type that shows the advanced pulmonary vascular changes described by Parker and Weiss (1936). The development of pure mitral stenosis in its early stages and its clinical course have been described by Walsh, Bland, and Duckett Jones (1940) among the large group of well-observed cases of rheumatic heart disease in Boston, and they found that the course was generally mild and the prognosis relatively good. This is, however, by no means the rule, and some of these patients with pure stenosis and rapidly progressive lung symptoms and signs are much more incapacitated than those who show a slower progression from passive congestion in the lungs to right-sided failure, often ushered in by auricular fibrillation. They present as lung failure rather than heart failure, their prognosis is poor, they respond poorly to medical treatment, and they often die from acute pulmonary oedema.

It is in this type with clinically pure and pathologically tight mitral stenosis that surgery is most indicated, for the lungs are mechanically gripped between the compensating force of a hypertrophied right ventricle and the increased pressure in the obstructed left atrium; the heart muscle is good, and it is primarily the stenosed valve that is at fault. Such cases have been selected for the venous-shunt operation; they are much more likely to get lasting improvement from mitral valvulotomy. The shunt operations that create a right-to-left venous fistula are certainly no less severe operations than valvulotomy; they offer no more than symptomatic relief, and do nothing to relieve the valvular obstruction and impaired efficiency of the right heart. Our successful cases all had these severe pulmonary episodes.

Recurrent severe haemoptysis may also be an indication for operation. Haemoptysis in mitral stenosis may be due to pulmonary embolism, most often associated with auricular fibrillation and failure. In cases without pulmonary infarction and with normal rhythm it may be an indication of the "cardiac lung." Massive haemoptysis may occur through rupture of dilated bronchial vessels which may be found in the pulmonary hypertension of mitral stenosis, or may be associated with attacks of pulmonary oedema due to left atrial failure (Bramwell and Jones, 1944). That it indicates a poor prognosis in cases of mitral stenosis without large hearts was shown by Wolff and Levine (1941); this stresses its importance as a symptom for considering surgery. In Case 5 it was the first indication of mitral stenosis, and was a feature of five of our eight cases.

Naturally, the degree of disability will be one of the main criteria in deciding if the risk of operation is justifiable. The younger patient is more likely to be suitable, provided recurrent or smouldering rheumatic carditis is absent. We have, however, operated successfully on one patient aged 42 and one aged 36; sometimes the older patients have been well compensated until recently—for example, the man aged 42 (Case 5) whose symptoms had been present for only three years.

The information obtained by cardiac catheterization is of great importance (see Table II). The changes following moderate exercise should also be measured. Thus Case 6 showed a rise in pulmonary arterial pressure after exercise (100/78 mm. Hg) even though the pressure had been high at rest (79/44 mm. Hg); his cardiac output on exercise rose only from 2.2 to 2.8 litres a minute. In Case 7 the pulmonary pressure was moderately raised at rest but rose sharply after exercise, with a fall in cardiac output.

Changes in these data after mitral valvulotomy should provide valuable information. Apart from the clinical improvement that follows operation it is important to study the changes that can occur in the secondary pulmonary hypertension. If this can be lowered and kept low by operation it will say much for the success of valvulotomy. If it remains high the later results of the operation will be disappointing.

It is in cases such as Case 7, in which the resting pressure in the pulmonary artery is low but there is a sharp rise

after exercise, that we can expect the best results. Such a finding is an indication for operation, since a permanent rise in pulmonary pressure is likely unless the mitral obstruction is relieved.

We feel that the immediate good results in all the six successful cases and the maintenance of the good result in those which have been followed up for the longer times show that the operation is fully justified. It has been well tolerated even in those who were bad risks (Cases 1, 4, 5, 6, and 8). The evidence provided by this experience is as yet small, but it is large enough to justify recommending and performing the operation in other selected patients.

Summary

The attempts of 25 years ago to relieve mitral stenosis by direct operation upon the valve were followed by such bad results that the procedure fell into disfavour. The great advances in thoracic surgery since then, and the recently demonstrated feasibility of direct operation upon the pulmonary valves of the heart, have pointed to the time being ripe for reconsideration of this important problem.

From a large number of patients with mitral stenosis careful selection has been made of eight who were seriously incapacitated and deteriorating. These eight have been submitted to mitral valvulotomy, with six successes and two deaths. The first was operated upon in September, 1948.

Direct relief of the valvular obstruction has been preferred to the various indirect methods, usually some form of venous shunt. These indirect operations aim only at symptomatic relief and are at least as severe as valvulotomy, which aims at achieving some degree of cure.

The valve is better approached through the left auricular appendage than through the left ventricle.

The contraction of the stenosed valve is discussed and the importance of enlarging the opening along the line of the commissures is demonstrated. In this way it is possible, in addition to increasing the opening, to reconstruct, in some degree, two valve flaps; these by virtue of their increased mobility are not likely to encourage regurgitation, but may even reduce it. The manipulations are well tolerated and in most cases the valve can be split with the finger, or the finger can be used to carry a valvulotome.

The most suitable cases are those with pure mitral stenosis and a reasonably good myocardium, with progressive lung symptoms and signs, but before pulmonary hypertension is too far advanced.

Contraindications are rheumatic activity or the likelihood of this, associated aortic regurgitation or much mitral regurgitation, gross enlargement of the heart or of the left atrium, or auricular fibrillation or congestive failure, when these are of long standing.

Cardiac catheterization gives valuable help in the assessment of these patients, especially as regards the pressure in the pulmonary artery and the changes in this and in cardiac output, with and without exercise, before and after operation.

The six survivors have all been much improved and have been able to walk farther and do more without provoking cardiac asthma or pulmonary oedema; some have already returned to work that they could not manage before.

The results in this small series are good enough to show that valvulotomy for mitral stenosis is a thoroughly practical procedure and can now be justifiably recommended in suitable cases.

Only patients with a grave outlook have so far been selected, but the encouraging results make us hope that surgery may be indicated in some less advanced cases.

[Since this paper was written another successful case has been operated on for Dr. Paul Wood. The patient, a woman aged 34, had severe secondary pulmonary hypertension. This makes a total of nine cases with seven successes.]

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PHARMACOLOGY OF D-O.O-DIMETHYL TUBOCURARINE IODIDE IN RELATION TO ITS CLINICAL USE

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The preparation from D-tubocurarine of its dimethyl ether, D-O.O-dimethyl tubocurarine iodide, was first described by King (1935). In recent years a number of workers have investigated the properties of this compound in experimental animals, and several groups of authors have reported its administration to man (Marsh *et al.*, 1948; Stoelting *et al.*, 1948; Pelikan *et al.*, 1950; Wilson *et al.*, at p. 1296 of this issue).

TABLE I.—*Ratio of Potency of* D-*O.O-dimethyl Tubocurarine Iodide to* D-*Tubocurarine Chloride*

Reference	Mouse	Rat	Guinea-pig	Rabbit	Cat	Man
Dutcher (1946) ..				9 (HD)		
Glock *et al.* (1948)	0·5 (LD)	3 (LD)	2 (LD)	9 (LD)		
Collier *et al.* (1948)	0·7 (RR50)	4 (RR50)		10–11 (RR50)		
Marsh *et al.* (1948)		8 (LD50)		7·5 (HD)	7 (SG)	5 (HD)
Swanson *et al.* (1949)	0·6 (LD50)	5 (SG)		8 (HD)	5–7 (SG)	
Pelikan *et al.* (1950)	0·7 (LD50)			8 (HD)	6·5 (RR)	2·3 (GD)

HD = Head-drop; GD = decline in grip strength; LD = lethal dose; RR = loss of righting reflex; SG = sciatic-gastrocnemius preparation.

As will be seen from Table I, which summarizes results in the published literature, D-dimethyl tubocurarine iodide is considerably more active than D-tubocurarine chloride in all mammals tested, except the mouse.

The great activity of the dimethyl ether of tubocurarine, the fact that its action is of considerable duration, and the notably favourable margin which exists between the effective dose (ED) and the lethal dose in rat and rabbit (Collier *et al.*, 1948) suggested that this compound might have some clinical use. The present paper summarizes experiments in animals, both published and unpublished, which appear to bear on the possible clinical use of dimethyl tubocurarine.

Antagonism by Neostigmine

Swanson *et al.* (1949) found that neostigmine antagonized dimethyl tubocurarine in the rabbit and dog. Antagonism was moderate if the two drugs were administered to the rabbit simultaneously. Antagonism was weak in the dog and rabbit if dimethyl tubocurarine was administered before neostigmine.

We have investigated how far neostigmine antagonizes dimethyl tubocurarine in the rabbit, the rat, and the mouse, and we have compared the antagonism of the dimethyl derivative with that of the parent alkaloid. In all experiments the abolition of the normal righting reflex was used as the criterion of curarization. Neostigmine was administered intravenously just before the curarizing drug was given by the same route.

The Rabbit.—In one experiment it was found that 0.05 mg. of neostigmine per kg. doubled the minimal effective dose of D-tubocurarine. This result agrees reasonably well with that of Chase *et al.* (1947), who found that 0.05 mg. of neostigmine per kg. raised the head-drop dose for the rabbit by a factor of 2.6, while 0.025 mg. of neostigmine per kg. raised the dose by a factor of 1.3. In an experiment with dimethyl tubocurarine it was found that 0.05 mg. of neostigmine per kg. raised the minimal effective dose of dimethyl tubocurarine by a factor of 10. In a further experiment 0.025 mg. of neostigmine per kg. raised the effective dose by a factor of 2.5. From these experiments, which are summarized in Table II, it appears that neostigmine antagonizes dimethyl tubocurarine at least as readily as it antagonizes D-tubocurarine in the rabbit.

TABLE II.—*Antagonism of D-Tubocurarine and Dimethyl Tubocurarine by Neostigmine in the Rabbit*

Experiment	No. of Rabbits	Neostigmine (mg. per kg. I.V.)	Curarizing Drug	Factor by which Minimal Effective Dose is Raised
M.35 ..	8	0·05	D-Tubocurarine	2
M.36 ..	9	0·05	Dimethyl tubocurarine	10
M.37 ..	13	0·025	" "	2·5

The Rat.—Experiments in rats, weighing 50 to 100 g., showed that an intravenous dose of 0.05 mg. of neostigmine per kg. raised the ED 50 of D-tubocurarine by a factor of 2.2, while the same dose of neostigmine raised the ED 50 of the dimethyl derivative by a factor of 2.3. These experiments are summarized in Table III.

TABLE III.—*Antagonism of D-Tubocurarine and Dimethyl Tubocurarine by Neostigmine in the Rat*

Experiment	No. of Rats	Neostigmine (mg. per kg. I.V.)	Curarizing Drug	ED 50 Curarizing Drug (μg. per kg. I.V.) with Standard Error	Ratio of ED 50s with and without Neostigmine
M.38	24	—	D-Tubocurarine	60·7 ± 2·75	2·2
	21	0·05		135·8 ± 12·91	
M.39	20	—	Dimethyl tubocurarine	10·8 ± 0·53	2·3
	20	0·05		25·0 ± 2·86	

The Mouse.—Preliminary experiments in mice indicated the use of a lower dose of neostigmine than that employed in the rat and rabbit. A dose of 0.01 mg. of neostigmine per kg. raised the ED 50 of D-tubocurarine in young mice by a factor of 1.5, and raised the ED 50 of dimethyl tubocurarine by a factor of 1.2. The results of tests in young mice are summarized in Table IV.

TABLE IV.—*Antagonism of D-Tubocurarine and Dimethyl Tubocurarine by Neostigmine in the Mouse*

Experiment	No. of Mice	Neostigmine (mg. per kg. I.V.)	Curarizing Drug	ED 50 Curarizing Drug (μg. per kg. I.V.)	Ratio of ED 50s with and without Neostigmine
M.40	20	—	D-Tubocurarine	114·8 ± 5·31	1·5
	27	0·01		171·8 ± 5·26	
M.41	32	—	Dimethyl tubocurarine	162·2 ± 2·67	1·2
	47	0·01		194·1 ± 7·19	

Release of Histamine

It is well known that the administration of D-tubocurarine is apt to result in the release of histamine or of a like-acting substance in man. Grob *et al.* (1947), who have investigated this question experimentally, believe that curare preparations are apt to release histamine in some individuals to an extent which may be serious in practice. For this reason it is of interest to inquire how far dimethyl tubocurarine releases histamine when administered to experimental animals, and how it compares with tubocurarine in this respect.

MacIntosh and Paton (1949) have reported that, in the cat with autonomic ganglia blocked chemically, an intravenous dose of 0.6 mg. of either D-tubocurarine or its dimethyl ether per kg. is just sufficient to release histamine detected by its effect on the animal's blood pressure (delayed depressor effect). Further unpublished experiments of the same type (Paton, 1948, private communication) confirm that dimethyl tubocurarine is not more active than the parent alkaloid in liberating histamine.

Heymans *et al.* (1949) have given curarizing doses of dimethyl tubocurarine to two dogs. In neither animal was the arterial blood pressure depressed or the physiological mechanism of blood-pressure regulation disturbed.

Blocking of Autonomic Ganglia

It is known that tubocurarine to some extent interrupts conduction in autonomic ganglia in the experimental animal. Paton (1948) has carried out some experiments to compare the extent to which dimethyl tubocurarine and tubocurarine itself block the superior cervical ganglion of the cat. The animal was prepared so that the preganglionic cervical sympathetic fibres were stimulated electrically at a frequency of 10 shocks a second and the contraction of the nictitating membrane was recorded on smoked paper.

Administration of heavy doses of D-tubocurarine and of its dimethyl ether caused a detectable lessening of tension in the nictitating membrane. Tracings obtained in experiments on two cats showed that, weight for weight, dimethyl tubocurarine was no more, possibly less, active in blocking the superior cervical ganglion than was tubocurarine.

Effects of Repeated Administration

Stoelting *et al.* (1948) administered intravenously 0.0167 mg. of dimethyl tubocurarine per kg. daily for ten days to eight rabbits. This dose represented the average dose sufficient to produce head-drop in their previous experiments. All rabbits survived this dose, and at the end of the period they were given an intravenous LD 50 of the drug. This proved fatal in six out of eight animals, suggesting that neither tolerance nor sensitiveness to the compound

had increased. A similar experiment with similar results is reported by Swanson *et al.* (1949).

We performed one experiment in the rat in which we obtained rather similar results. Intravenous doses of twice the ED 50 (27 μg. per kg.) were given to ten rats once or twice daily for three successive days. The dose given on the third day killed one of the ten animals; one was not paralysed; and the remaining eight were paralysed for periods varying between 3 and 11 minutes, which was normal for the dose of drug given.

Administration with Anaesthetics

The question naturally arises whether dimethyl tubocurarine can be safely administered with an anaesthetic. We have performed a certain number of experiments in rats to investigate this point.

In these experiments dimethyl tubocurarine in effective doses was administered to rats together with effective doses of either thiopentone or ether, the duration of paralysis was timed, and the general effects on the animal were noted. Thiopentone was administered intravenously, and rats were exposed for a measured period of time to air saturated with ether vapour. Loss of the righting reflex was taken as an indication either of narcosis or of curarization, without attempting to distinguish between the two processes. It will be seen from Table V that dimethyl tubocurarine can be given in effective doses with effective doses of thiopentone or ether without untoward results. A combination of dimethyl tubocurarine and ether together, however, has a greater effect than either separately, since the difference in the duration of paralysis in experiment M.34 proves to be significant.

TABLE V.—*Effects of Administration of Dimethyl Tubocurarine with Anaesthetics*

Experiment	No. of Rats	Thiopentone (mg. per kg. I.V.)	Time Exposed to Ether (Sec.)	Dimethyl Tubocurarine (μg. per kg. I.V.)	Mean Duration of Paralysis (Min.)	Standard Error	Comments
M.32	12	15	—	—	10·0	±2·15	
	10	—	—	15	4·4	±0·68	
	12	15	—	15	9·0	±1·62	Satisfactory recovery
M.34	10	—	60	—	1·1	±0·26	2 rats not narcotized
	9	—	—	20	9·0	±0·91	2 rats died
	10	—	60	20	15·0	±1·77	2 rats died. Rest recovered satisfactorily

Swanson *et al.* (1949) found that the toxicity of dimethyl tubocurarine to dogs was greatly increased by ether and slightly increased by pentobarbitone.

It is noteworthy that Stoelting *et al.* (1948) have administered dimethyl tubocurarine to 100 successive patients without mishap. In their series of cases 16 patients were anaesthetized with cyclopropane, 49 with ether, and 35 with nitrous oxide. Wilson *et al.* (1950) have likewise reported the successful administration of dimethyl tubocurarine together with thiopentone and nitrous oxide and oxygen in 100 operations.

Discussion

It appears to be clear from the above results that dimethyl tubocurarine is similar in many respects to tubocurarine. While dimethyl tubocurarine is undoubtedly capable of liberating histamine and of blocking autonomic ganglia, it seems certain that weight for weight it is no more and possibly less active than tubocurarine itself. Since dimethyl tubocurarine is considerably more active in curarizing man than tubocurarine itself, we may expect a curarizing dose of the dimethyl derivative to be proportionately less likely to release histamine or to hamper conduction in the autonomic ganglia.

From the experimental evidence presented it seems likely that dimethyl tubocurarine can be given with success in association with an anaesthetic.

In some species of experimental animals dimethyl tubocurarine has a more prolonged action than tubocurarine. It appears from the work of Pelikan, Sadove, and Unna, however, that in man its action is of slightly shorter duration than that of tubocurarine. These workers found that in man, as in rabbits, dimethyl tubocurarine depresses respiration relatively less than D-tubocurarine or decamethonium iodide.

Summary

Dimethyl tubocurarine is a considerably more effective curarizing agent than tubocurarine in the rat, guinea-pig, rabbit, and cat. The dimethyl derivative is less active than the parent compound in the mouse.

Neostigmine antagonizes dimethyl tubocurarine in those animal species investigated—namely, the mouse, rat, and rabbit.

Weight for weight dimethyl tubocurarine is no more active than tubocurarine in liberating histamine in the cat.

Weight for weight dimethyl tubocurarine is no more active in blocking autonomic ganglia than tubocurarine in the cat.

There is no evidence of increased sensitiveness or tolerance if dimethyl tubocurarine is administered repeatedly to the rabbit or rat.

Dimethyl tubocurarine has been administered successfully to the rat with ether and with thiopentone. There is some synergism between ether and dimethyl tubocurarine.

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It is announced from Stockholm that for the purposes of research into poliomyelitis 400 monkeys from Java will be imported shortly by Professor Sven Gard, of the Carolinian Institute, Stockholm. The chief object of this research will be to determine as closely as possible the number of virus hosts during an epidemic and to obtain concrete evidence that healthy persons are moving around as virus hosts and sources of contagion.

DIMETHYL ETHER OF D-TUBOCURARINE IODIDE AS A CURARIZING AGENT IN ANAESTHESIA FOR THORACIC SURGERY

BY

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Until comparatively recently the favourite agent for producing anaesthesia for thoracic operations has probably been cyclopropane. The use of this gas, combined with controlled respiration and carbon dioxide absorption, reduces the movements of the diaphragm to a minimum and so gives a tranquil field of operation. On the other hand, the highly explosive nature of cyclopropane greatly restricts or entirely prevents the use of any form of diathermy during its administration. This is a real handicap to the surgeon and tends appreciably to prolong operations. Another disadvantage is the possible occurrence of the so-called cyclopropane shock in the immediate post-operative stages.

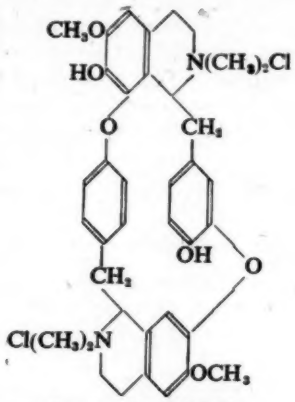
With the introduction of curare and other similar agents a still better anaesthetic technique has become available for these operations. With this new method, general anaesthesia is obtained by the use of soluble thiopentone in combination with nitrous oxide and oxygen in closed circuit with a soda-lime canister for carbon dioxide absorption. The necessary diaphragmatic paralysis is obtained by intermittent doses of D-tubocurarine chloride, and diathermy can be freely used at all stages of the operation without danger of explosion.

Careful case records taken in a busy thoracic unit showed that, while this D-tubocurarine technique represented a great advance on previous methods, it had some disadvantages. These, though not unduly restricting its use, suggested that some other curarizing agent might be discovered which would approach the ideal more nearly still.

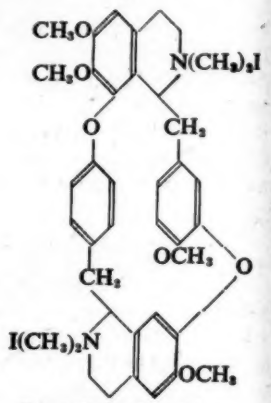
Some months ago one of us (H. B. W.) was given the opportunity, through the Joint Anaesthetics Committee of the Medical Research Council and the Royal Society of Medicine, to carry out a clinical investigation of a new product, the dimethyl ether of D-tubocurarine iodide, with a view to determining whether it had advantages over D-tubocurarine chloride, particularly in two respects: Did it release or facilitate the release of histamine to a less extent? and, Did it have less effect in paralysing autonomic ganglia?

Pharmacology

The dimethyl ether of D-tubocurarine iodide is obtained by treating D-tubocurarine chloride with two molecular equivalents of sodium hydroxide and then with two molecular equivalents of methyl iodide, all in methanol solution (Collier, Paris, and Woolf, 1948); the two free hydroxyl groups are thus methylated, and the salt is changed from the chloride to the iodide. These differences are shown in the following structural formulae.



D-tubocurarine chloride



Dimethyl ether of D-tubocurarine iodide

Much animal experimentation has been carried out with this drug, both in this country by Collier, Paris, and Woolf (1948), and in the U.S.A. by Swanson, Henderson, and Chen (1949) and others; this work is reviewed in the article by Collier and Hall at p. 1293 of this issue. As might be expected from its chemical structure, the pharmacology of the new preparation is generally similar to that of D-tubocurarine chloride; but in the rabbit and cat it has been found to be seven to ten times more potent, and in some species its action is more rapid and prolonged. There is evidence, too (Collier and Paton, personal communication), that it is no more active in releasing histamine and in paralysing autonomic ganglia. In man the drug has been used as an adjunct to anaesthesia in 100 cases reported by Stoelting, Graf, and Vieira (1948).

With this evidence before us it seemed justifiable to try it in the thoracic unit, and to employ it for a period as the curarizing agent in major chest operations in place of D-tubocurarine chloride.

On examination of our previous records, when D-tubocurarine chloride had been used we had observed that after a period of two and a half to three hours there was a fairly constant depression of the systolic blood pressure accompanying a rise in the diastolic pressure—and this in spite of blood replacement. We had concluded that it might be due to histamine release from devitalized tissues facilitated by the presence of D-tubocurarine chloride in the circulation. Acting on this assumption, we began an investigation into the value of antihistamine drugs given in combination with D-tubocurarine chloride, with the object of counteracting the effects of histamine release. This will be the subject of a further paper at a later date.

The Investigation

The anaesthetic technique employed in our investigation into the value of the dimethyl ether of D-tubocurarine chloride was identical with our previous practice. It consisted of premedication with "omnopon" and scopolamine in orthodox dosage, induction of anaesthesia with soluble thiopentone, injection of dimethyl ether of D-tubocurarine iodide, and intubation under direct vision with as large a cuffed endotracheal tube as could be conveniently used. A 50:50 mixture of nitrous oxide and oxygen was then administered in a closed circuit with an intentional slight leak. Light-plane anaesthesia was maintained by fractional doses of soluble thiopentone introduced into the blood-transfusion tubing, and a quiet diaphragm achieved by

giving repeated doses of dimethyl ether of D-tubocurarine iodide by the same route.

We have based the dosage of the dimethyl ether of D-tubocurarine iodide on body weight; it has initially been of the order of 1 mg. per stone (6.35 kg.). We feel that it is safer to dose a patient adequately than to underdose him with any curarizing agent, to lessen the tendency to bronchospasm. Incremental doses of the dimethyl ether of D-tubocurarine iodide are of the order of 3 mg., and their administration is guided by the degree of diaphragmatic activity.

We were impressed by one striking improvement in our results on changing to the new compound—namely, the extreme ease with which a lung or lobe which had been allowed to collapse could be reinflated. Using D-tubocurarine chloride we had always been able to reinflate a lung or lobe, but quite firm pressure on the bag was often required, more particularly in the later stages of the operation. Using dimethyl ether of D-tubocurarine iodide, however, we found that the pressure required to reinflate the lung was much less and remained so throughout the operation. What is the explanation? Is it that when using D-tubocurarine chloride an excess of circulating histamine, with its tendency to increase bronchial muscle tone, is released as the operation proceeds and trauma increases, and that with the use of dimethyl ether of D-tubocurarine iodide there is less histamine release and consequently less stimulation of the tone of the bronchial tree?

There was also a definite change in the blood pressure picture. The fall in systolic blood pressure with an accompanying rise in diastolic pressure previously noticed did not seem to occur to the same extent, or, if it did, was manifest only at a much later stage than with D-tubocurarine chloride.

Conclusions

Owing to the absence, through illness, of one of us (H. B. W.), this communication is not as complete as we would desire and should be regarded as an interim report. With that limitation, our conclusions from using the dimethyl ether of D-tubocurarine iodide as the curarizing agent in 100 cases of major intrathoracic procedures, including pneumonectomies, lobectomies, and mediastinal tumours, are as follows:

1. Dimethyl ether of D-tubocurarine iodide seems to be 2 to 2½ times more potent than D-tubocurarine chloride.

2. The duration of action on diaphragmatic activity is a little shorter than with D-tubocurarine chloride and subsequent doses are required at intervals of 20 to 25 minutes.

3. Clinically there seems to be less release of histamine, as is evidenced by (*a*) maintenance of systolic and diastolic blood pressures, and (*b*) ease of inflation of collapsed lung tissues, particularly at the later stages of the operation.

4. In all other ways, as would be expected, the two preparations seem similar in action.

Recent work by Pelikan, Sadove, and Unna (1950) on the relative potency of D-tubocurarine chloride and the curare-like drugs gives support to our clinical findings on the relative strengths of D-tubocurarine chloride and the dimethyl ether of D-tubocurarine iodide, as it does to the relative duration of action of these preparations.

Our impressions are that in the dimethyl ether of D-tubocurarine iodide we have a curarizing agent which has all the advantages of D-tubocurarine chloride and which, from our small series of cases, seems to have less tendency towards histamine release. In no case had we any cause for anxiety, either on the table or post-operatively, which could be referred to the use of dimethyl ether of D-tubocurarine iodide. However, as of passing interest, it may be noted that in one recent thoracotomy, using D-tubocurarine chloride, a frank bronchospasm occurred and was confirmed by bronchoscopy. Fortunately it responded to appropriate measures.

No evidence of delayed detoxication of the dimethyl ether of D-tubocurarine iodide has been noted, nor have we seen any undue reactions to the drug. The possibility of idiosyncrasy to iodides should, however, be borne in mind when administering it.

The dimethyl ether of D-tubocurarine iodide used in this study was provided by Allen and Hanburys Ltd. through the Joint Anaesthetics Committee of the Medical Research Council and the Royal Society of Medicine.

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NINE BLOOD-GROUP ANTIBODIES IN A SINGLE SERUM AFTER MULTIPLE TRANSFUSIONS

BY

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The complete case record upon which this paper is based presents many facets that might be explored with interest by specialists in various fields of medicine and biology. One of the most striking features concerns the large number of antibodies this splenectomized patient was able to produce in response to a comparatively small number of transfusions administered at irregular intervals over a period of several years. Briefly the history is as follows.

Case History

Mrs. F. W., a 40-year-old white housewife, was first admitted to the Waterbury Hospital in September, 1933, for delivery. This was her second pregnancy, the first having terminated with toxaemia and premature stillbirth. After normal delivery of a normal child it was discovered that she had a large spleen. This she stated had been present for 12 years. She was readmitted for splenectomy in March, 1937. Blood studies on three occasions before splenectomy showed no anaemia or other evidence of blood dyscrasia. The spleen weighed 1,100 g., and increased fibrous tissue with many scattered islands of myelopoiesis and erythopoiesis were seen microscopically. Also many megakaryocytes were noted. Splenectomy was followed by mild anaemia, for which two blood transfusions were given without reaction.

During the next 12 years the patient was repeatedly admitted for anaemia and received several transfusions, as indicated in

Table I. She developed a leuco-erythroblastic peripheral blood picture with corrected white counts in the neighbourhood of 100,000. Her liver enlarged to fill most of the abdomen.

TABLE I.—*Blood Transfusions of Patient F. W.*

	No.	Donors (All Group O)	Reaction
March, 1937	1	Rh?	None
	2	Rh?	,,
Feb., 1945	3	Rh+ (anti-D)	,,
	4	Rh+ ,,	,,
	5	Rh+ ,,	,,
	6	Rh+ ,,	,,
April, 1946	7	Rh+ ,,	,,
	8	Rh+ ,,	,,
	9	Rh+ ,,	,,
	10	Rh+ ,,	,,
	11	Rh+ ,,	Chill and fever, nausea and vomiting
	12	Rh+ ,,	Mild haemolytic
	13	R$_1$r (anti-C–D–E)	None
	14	R$_1$r ,,	,,
Jan., 1949	15	R$_1$r ,,	,,
	16	R$_1$r ,,	,,
	17	R$_1$r ,,	,,
	18	R$_1$r ,,	,,
	19	R$_2$r ,,	Mild haemolytic
July, 1949 ..	20	R$_2$r ,,	Mild febrile

X-ray therapy over her liver resulted in prompt reduction of both red blood cell count and white count. In 1946 attempts to obtain a satisfactory cellular bone marrow by aspirations of the sternum, the right iliac crest, and a spinous process all failed. Skeletal radiographs revealed increased density of many bones with destruction of the normal trabecular pattern. A diagnosis of osteosclerosis and extramedullary haematopoiesis was made. She developed a bleeding peptic ulcer in 1948 and thereafter received a number of additional transfusions. Her transfusion history is set forth in Table I.

Thus it is seen that in a series of 20 transfusions reactions followed Nos. 11, 12, 19, and 20. It was found in 1949 that the patient was Rh$_1$ (CDe) and was sensitized to E. It was also found that her serum agglutinated some Rh$_1$ bloods, so donors of type R$_2$r (cDe/cde) were chosen. When one of these produced a mild haemolytic reaction, samples of serum and later of whole blood were sent to Boston for more complete studies.

Serological Details

Nine blood-group antibodies were identified in the serum of this patient (Table II). Since four of the antibodies had each been reported on fewer than eight previous occasions

TABLE II.—*The Blood Groups of Patient F. W. and the Antibodies in Her Serum*

System	Phenotype	Genotype	Antibodies in the Serum
ABO	O	OO	Anti-A and anti-B
MNS	MsMs	MsMs	Anti-N and anti-S
Rh		CDe/cde or CDe/cDe	Anti-E and anti-C^w
Kell	K–	kk	Anti-K
Lewis*	Le(a– b–)	?Le^{c}Le^c	Anti-Le^a and anti-Le^b
P	P–	pp	—
Lutheran* ..	Lu(a–)	Lu^{b}Lu^b	—

* For notation see Andresen *et al.* (1949).

it is clear that she showed extraordinary powers of antibody production. Such versatility has only once before been recognized, when seven blood-group antibodies were found in the serum of a woman suffering from lupus erythematosus diffusus who had been transfused on a number of occasions (Callender and Race, 1946).

Circumstances caused the serum (F. W.) to be investigated before the full groups of the patient's red cells were determined. This resulted in a situation, probably unique, in which it was possible to tell from the serum the ABO, MNS, Lewis, and Kell groups of the patient and to make a very good guess at the Rh group.

The antibodies are all to be found together in one sample of serum. Five of the antibodies are very rare ones, for at the time of their recognition in this serum anti-C^w had been found on four previous occasions, anti-S on five, anti-K on five, anti-N on seven, and anti-Le^b on about ten.

In view of the results of agglutination tests in saline at different temperatures, tests in albumin, and indirect anti-globulin tests, it seems certain that the anti-E and anti-K were immune antibodies. The anti-S, anti-C^w, and anti-Le^a all reacted more strongly at room temperature (17° C.) than at 37° C., and all reacted weakly in albumin; by use of the indirect anti-globulin test the anti-S gave a strong positive reaction, and the anti-C^w and anti-Le^a were weakly positive. It seems probable that these three antibodies were immune in origin. The anti-N and anti-Le^b were definitely cold agglutinins and may not have been immune.

Method of Investigation

At the Blood Grouping Laboratory, Boston, tube tests with undiluted serum and saline suspensions of 14 fully grouped and selected blood samples were carried out at 4° C., 17° C., and at 37° C. Tests against the same cells in albumin were also done at 37° C. The results of the albumin tests most clearly showed that anti-E was present. The serum was then tested against 10 samples of cde/cde in saline; at 17° C. all but one of the samples were agglutinated, the one sample being the only S negative in the 10. This made it almost certain that anti-S was present, and this was later proved to be so. The serum was then tested against cells lacking the antigens E and S, and the indirect globulin method showed that anti-K was present.

It was realized that there were still more antibodies present, but the supply of serum was exhausted. About three months later a second sample of serum was obtained, which was dried and sent to England for further investigation.

The presence in the reconstituted serum of anti-E, anti-S, and anti-K was confirmed. The serum was then tested at 17° C. against eight saline suspensions of blood lacking the antigens E, S, and K, and three of the samples were agglutinated: two of these were Le(a+), the third was Le(a–) but contained the antigen C^w. Indirect anti-globulin tests were weakly positive with the two Le(a+) samples and negative with the C^w sample. This suggested that these three reactions were due to two antibodies—probably anti-Le^a and anti-C^w. Cross absorptions and tests on selected samples of blood confirmed this. Re-inspection of the Boston protocols showed that the anti-C^w had at that period been giving a weakly positive anti-globulin reaction.

Tests carried out on a tile resting on ice showed that anti-N was present. The cells used were all Le(a–), E–, C^w–, K–, and S–. The anti-N reaction reached its maximum in 20 minutes.

Next 15 samples of cells which were Le(a–), E–, C^w–, K–, S–, and N– were tested, again on an iced tile, in a moist atmosphere: positive reactions were long-delayed, but were definite after 40 minutes and showed the presence of anti-Le^b. By other methods no positive reactions with the 15 cell samples could be detected.

Discussion

The recognition of such predisposition to make blood-group antibodies as that shown by the patient with osteosclerosis and extramedullary haematopoiesis, and by the patient previously described suffering from lupus erythematosus diffusus, raises a number of questions which cannot at present be answered. Were these two patients born

with a particularly alert antibody-forming system? If so, was this a contributing cause of their two obscure diseases? Or is the sensitivity secondary to the disease? Or is there no connexion between the diseases and the presence of the antibodies other than the fact that the diseases made repeated transfusions necessary, and so gave the patients a chance to demonstrate powers that may not be very uncommon?

The patient possesses antibodies to all the antigens which she lacks in five blood-group systems. The evidence for the presence of each antibody was examined statistically. Sufficient samples of red cells were tested to reduce to a very low degree of probability the chance that any of the reactions were merely coincidental.

Several of the antibodies in this serum were weak and might have disappeared on heterospecific absorption. The need for absorption could be overcome by the use of highly selected red cell samples; these were chosen from a large panel of some 400 persons grouped for the A_1A_2BO, MNS, P, Rh, Lutheran, Kell, and Lewis systems.

Since the patient lacks the antigen P it is surprising that no anti-P could be found in her serum, for this antibody is of much more frequent occurrence (Henningsen, 1949) than most of those which were identified; moreover, she must surely have received some P+ blood. In view of the demonstration by Mainwaring and Pickles (1948) that Lutheran is quite an effective antigen, it would seem possible that the patient did not receive any Lu(a+) blood.

It was rather disappointing that no "new" blood-group antibodies could be demonstrated in this serum. The search, however, was greatly limited by the rarity of blood samples compatible with the antibodies known to be present in the serum.

Summary

A patient suffering from osteosclerosis with extramedullary haematopoiesis and who had been transfused 20 times was found to have nine blood-group antibodies in her serum; these were anti-A, anti-B, anti-N, anti-S, anti-E, anti-C^w, anti-K, anti-Le^a, and anti-Le^b. Five of these antibodies are very rare.

We wish to thank Dr. L. K. Diamond, of the Blood Grouping Laboratory, Boston, for making it possible for one of us (R. S.) to work there for a time. We also thank Dr. B. H. Kirman and Mr. J. E. Stevens, of the Fountain Hospital, Tooting, for their help in setting up the large panel of control cells.

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The British Rheumatic Association, which is a voluntary body working with the goodwill of the Ministry of Health to improve the medical, social, and economic position of sufferers from rheumatism, has formed a financially independent association called B.R.A. Homes, Ltd.—a registered housing society with charitable status. The society is in need of funds to equip a Georgian crescent (St. Ann's) at Buxton, Derbyshire, with 60 amenity beds for those who cannot get urgently needed treatment in hospital but who can receive it at St. Ann's as out-patients under the Health Act. There will also be 30 furnished flatlets for elderly disabled sufferers from rheumatism needing nursing care. St. Ann's will receive patients from all parts of the country, but it is hoped to open similar homes later elsewhere. A total sum of about £50,000 is needed, and contributions will be gratefully accepted by B.R.A. Homes, Ltd., at 5, Tite Street, London, S.W.3.

MULTIPLE ANTIBODY RESPONSE TO REPEATED TRANSFUSIONS

BY

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AND

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As our knowledge of red cell antigens and antibodies increases so the selection of blood suitable for transfusion from one individual to another becomes an undertaking of increasing complexity. The routine cross-matching tests carried out in hospital practice are usually sufficient to detect the presence of the antigens A, B, O, and D and the corresponding antibodies when performed by trained and competent medical officers or technicians. Where, however, repeated transfusions are required the risk of immunization or a transfusion reaction due to the rarer antibodies, which are not readily detectable by such techniques, is one that cannot be ignored. In such cases cross-matching calls for special techniques, and the search for and identification of the rarer antibodies may become an arduous and complex task best suited to laboratories specially equipped for carrying out investigations of this nature.

While certain individuals are more readily immunized by blood antigens than others, it is reasonable to suppose that the greater the number of transfusions given to a patient the greater is the likelihood of his developing antibodies of one sort or another; and with the continuing popularity of multiple transfusions as a therapeutic measure in certain diseases and the introduction of new techniques for antibody detection it is becoming increasingly clear that the so-called "rare" antibodies are of much more frequent occurrence than is generally believed.

The case reported here is one of several encountered during the past few months in which "rare" antibodies have developed as a result of repeated transfusions. It illustrates multiple antibody response to the transfusion of blood from 24 donors, all of whom were "compatible" in respect of the A, B, O, and D blood antigens.

Case Report

The patient, a widow aged 64 with four normal children, had no history of miscarriages or of any transfusions of blood. She complained of lassitude, dyspnoea, and oedema of the ankles of six to eight months' duration and of passing very dark urine.

On examination on September 2, 1949, there was profound anaemia but no icterus. The red cell count was 1,280,000 per c.mm., haemoglobin 25%, serum bilirubin 3.3 mg. per 100 ml. The spleen was palpable and the liver "(?) slightly enlarged." The heart was slightly enlarged to the left, with an apical systolic murmur. A provisional diagnosis of acquired haemolytic anaemia was made.

On September 24 a specimen of her blood was received at the Sheffield Blood Transfusion Centre with a request for two pints (1.14 litres) of packed cells. Her cells were found to be Group A Rh-positive, and no difficulty was encountered in matching her serum against the cells of four D-positive donors in saline and albumin suspension. Two pints of packed cells were transfused: the haemoglobin rose to 45%; the temperature, which had been swinging wildly up to this stage, settled down and she seemed very much better. She was transfused again on September 30 with good results.

Fourteen days later a further specimen was received and her cells were found to be A_1 D NNp. Her serum was tested against a panel of 10 Group O cells of various Rh types in saline and albumin at 37° C., room temperature, and 4° C., and an indirect Coombs test was performed. These tests were all negative, indicating that no Rh or cold agglutinins had been formed. The patient's serum was tested against her own cells at 4° C., room temperature, and 37° C., and a direct Coombs test was performed upon her washed cells. All of these were negative and no haemolysins were detected.

On October 16 her temperature again became irregular and definite icterus appeared. The spleen was much larger than before and the haemoglobin had dropped to 32%. Next day a further specimen of blood was received with a request for more packed cells, the hospital having reported difficulty in cross-matching. Four bottles were matched, two pints of whole blood dispatched as an emergency on the night of the 17th, and a pint (570 ml.) of packed cells next morning. The transfusion failed to stop the haemolytic process.

Further investigations were then undertaken on the sample of blood received on October 17. She was found to be Group A_1, NNS, ?P, R_1R_1 (CDe/CDe); Lewis, Lutheran, Kell, and Willis negative. It was suspected that the doubtful reaction with anti-P serum was due to transfused cells carrying the P antigen, as she had previously been found to be P-negative. The serum, which was very yellow (a condition not previously observed), was tested further for antibodies. On this occasion there was a visual positive reaction with Group O R″R″ (cdE/cdE) cells when incubated at 37° C., and in addition a positive reaction at 4° C. and room temperature against her own cells and against each of 16 O, two A_1, and two A_2 cells of various Rh types and including M positives and negatives and P positives and negatives. Weak reactions occurred with two cells lacking the M and E antigens. Doubtful reactions were noted when the patient's serum was placed against her own washed cells, and the direct Coombs test was weakly positive. It was difficult to decide whether this reaction was due to autoagglutinin or sensitized donor cells in the patient's circulation or to the haemolytic anaemia itself, but, in view of the weakness of the Coombs reaction and the doubtful autoreaction, the presence of donor cells was thought to be the more probable explanation. The serum definitely contained anti-E together with one or more antibodies reacting strongly with saline suspensions of all cells in the panel at 4° C. and room temperature, and weakly at 37° C. with some cells possessing the M but not the E antigen. Some strongly positive reactions occurred in albumin at 37° C., but only in the presence of the E antigen, and it was possible to distinguish by the strength of the reaction cells with a single dose of E from those with a double dose. The indirect Coombs test was positive with R_2R_2 (cDE/cDE) and R″R″ (cdE/cdE), but negative with R_2r (cDE/cde) cells.

E-negative packed cells were transfused on October 22, 28, and 30. Cross-matching was performed as before, using the saline, albumin, and Coombs methods, but it had become increasingly difficult to find cells which would match with her serum by all three methods.

These transfusions were without beneficial effect apart from increasing the haemoglobin content of the blood, and by October 28 the spleen had greatly enlarged and there was a marked increase of urobilinogen in the urine. Her general condition had deteriorated considerably and her heart was failing rapidly. She died on October 31. There was no evidence of a transfusion reaction after any of the transfusions given during her stay in hospital.

A post-mortem specimen of her blood was tested with anti-M, anti-N, and anti-P sera, and a positive reaction was obtained with each. With anti-M and anti-P, however, the clumped cells lay in a negative field, and since the patient's cells were originally typed as NNp it is almost certain that the clumping was due to donor cells. The specimen was allowed to stand at 4° C. for some hours in order to absorb any autoagglutinin that might be present, and the absorbed serum was tested against a panel of 12 Group O cells of various Rh and MNP types. The anti-E was again in evidence at 37° C. in both saline and albumin cell-suspensions and had a titre of 1 against cells with a single dose of E (NNR_2r) and 8 against those with a double dose (NNR_2R_2). It was also noted that at 37° C. the serum agglutinated saline suspensions of cells carrying the M antigen, irrespective of the presence or absence of E: in albumin, however, only the cells bearing E were agglutinated. At room temperature only two types of cells in the panel were not agglutinated —NNP and NNp—both E-negative. From these findings it was evident that anti-M had been formed. The titre of the anti-M at room temperature was found to be 4. At 4° C. the cell type NNP was agglutinated while NNp was not affected. This indicated that the serum contained anti-P in addition to anti-M and anti-E. The patient's serum was finally placed against her own cells, and while no reaction took place at 37° C. agglutination did occur at 4° C., the clumps appearing in the negative field; this is not surprising, since the specimen was to some extent composed of donor cells and gave positive reactions when tested with known anti-M and anti-P sera.

The post-mortem examination revealed marked splenomegaly with some hepatomegaly: focal necrosis of the liver with a fine cirrhosis of portal distribution. The spleen showed marked siderosis, very numerous histiocytes, and absence of lymphoid follicles, the whole gland being intensely engorged with blood. A diagnosis of haemolytic anaemia secondary to Banti's disease was made.

Summary and Conclusions

The patient, who was transfused in the course of a month with blood from 24 different donors, developed a rare antibody (anti-E), a very rare antibody (anti-M, active at 37° C.), and a specific cold antibody (anti-P).

The blood from all of these donors was "compatible" with respect to the A, B, O, and D blood antigens.

As routine methods of cross-matching are inadequate to detect the rarer antibodies it is advisable that special techniques should be employed in those cases in which repeated transfusions are likely to be required.

The details of the laboratory investigations given in this paper clearly show that the search for and identification of such antibodies can be successfully undertaken only in those laboratories where a panel of rare cells, samples of rare antibodies, and specially trained staff are available.

Systematic search for rare antibodies in patients who have received many transfusions of so-called compatible blood will reveal that these antibodies are of much more frequent occurrence than is generally believed.

We are greatly indebted to Drs. R. J. Twort and A. J. Bailey for the clinical notes and post-mortem findings in this case, and to Mr. I. Dunsford for guidance in the serological investigations.

A circular from the Ministry of Health to hospital boards and committees discusses the conditions in which hospital employees aged 15 to 18 should work. The following are among the duties in which they should not be employed: handling drugs or nursing sick people; working in operating theatres or mortuaries; working in homes for the dying, cancer hospitals, or V.D. hospitals or departments. They should not work in the wards of mental hospitals or mental deficiency institutions or in the *x*-ray, physical-medicine, or out-patient departments of mental hospitals, isolation hospitals, or tuberculosis sanatoria. Young persons under the age of 17 should not be employed in the *x*-ray, physical-medicine, or out-patient departments of maternity hospitals or in hospital reception rooms, nor should they be attached to wards in any type of hospital. Among the duties considered suitable for young persons the circular lists help with filing, care of linen, attending to the telephone, and clerical work. Hospital authorities should arrange for young persons employed by them to attend part-time courses of further education for the equivalent of one day a week, and this time should be paid for at the usual rates.

LIVER DAMAGE IN ULCERATIVE COLITIS

BY

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The occurrence of liver damage as a complication of chronic ulcerative colitis has been reported occasionally during the past twenty years (Bargen and Giffin, 1930; Comfort *et al.*, 1938; Tumen *et al.*, 1947; Ross and Swarts, 1948), and it has been suggested that there is an indirect relationship between the two conditions. Tumen *et al.* reported five examples in 151 consecutive cases of ulcerative colitis and suggested that the liver damage was probably due to the chronic state of malnutrition which is associated with this disease. He also noted that whereas cirrhosis of the liver is usually found in patients of middle age and over, and most commonly in men, in the cases which he reported the age was considerably less and three of the five were women. This argument in favour of a causal relationship between the two conditions is, however, exceedingly weak, as was pointed out in an annotation in the *British Medical Journal* (1949, **1**, 189). Any condition complicating ulcerative colitis, whether causally related or not, must of necessity have the same age and sex distribution as the disease itself.

It is, of course, quite possible that detectable liver damage may occur at some period of the disease and later recover. This may possibly explain the occasional but well-known finding of an enlarged spleen in ulcerative colitis when no other evidence of liver damage can be found. The significance of finger-clubbing, which is sometimes present in ulcerative colitis and in cirrhosis of the liver, is quite unknown, but its presence should certainly lead to an investigation of the liver function. It is now well established that diffuse hepatic fibrosis follows prolonged heavy infiltration of the liver cells with fat. It has been shown that this is due to a deficiency of certain lipotropic factors, principally methionine and cystine. For several reasons this deficiency may arise in cases of chronic ulcerative colitis. First, the rate of passage of the intestinal contents is increased, leading to incomplete digestion and absorption of food. Secondly, the patient's appetite in this disease is often grossly impaired and the diet therefore inadequate. Thirdly, it has sometimes been the case that inadequate diets have been prescribed in the mistaken idea that a low residue is being achieved. No such deficiency should arise provided that plenty of milk is allowed, and actually in most cases there is no reason to prohibit normal amounts of meat in the diet.

Three cases of ulcerative colitis which were associated with severe liver damage are described below. These have been seen during the past three years among approximately 20 cases. In the second case an ileostomy was performed, but it is clear that the liver was so severely damaged that the patient could not tolerate a major procedure. Whether or not an ileostomy, with the improved nutritional state which usually follows, should be performed in cases with lesser degrees of liver damage is problematical.

Case 1

A married woman aged 44 began to have diarrhoea with passage of blood in 1940; this continued without remission until 1942, when appendicostomy was performed. Diarrhoea continued, and in 1946 swelling of the abdomen started.

In April, 1947, she was admitted to hospital, where she was seen to be sallow and wasted, with slight oedema of the ankles and a grossly distended abdomen containing much free fluid. After the ascites had been tapped a firm smooth liver edge could be felt extending two to three fingerbreadths below the right costal margin. The spleen was also hard and extended about three fingerbreadths below the left costal margin. Two barium enemas revealed the usual changes of ulcerative colitis extending proximally to the splenic flexure. There was a moderate degree of anaemia; Hb, 75%; red cells, 3,370,000 per c.mm.; white cells, 6,800 per c.mm. Plasma proteins were 7 g.%—albumin 2.6 g., globulin 4.0 g., fibrinogen 0.4 g.%; alkaline phosphatase, 3 units per 100 ml.; indirect van den Bergh, 0.1 mg. bilirubin per 100 ml.

Case 2

A married woman aged 37 had a 12-years history of watery diarrhoea sometimes accompanied by the passage of blood. She became anaemic and took iron intermittently, but this seemed to aggravate the diarrhoea. In 1946 an adenoma of the thyroid was removed. In July, 1949, she was admitted to hospital complaining of great shortness of breath, swelling of the ankles, lassitude, and diarrhoea, with about ten loose or watery stools daily.

On examination she was apparently grossly anaemic, the tongue was smooth, and angular stomatitis was present. She was moderately well nourished, the fingers were clubbed, and the spleen was palpable two fingerbreadths below the left costal margin. The liver could not be felt and there was no ascites. There was slight oedema of the ankles.

Investigations.—Hb, 20%; red cells, 1,880,000 per c.mm.; white cells, 3,600 per c.mm. Stools were watery, without blood or mucus; and no pathogens were cultured. A barium enema revealed the changes of advanced ulcerative colitis in the whole of the colon. A fractional test meal disclosed histamine-fast achlorhydria. Plasma proteins amounted to 7.2 g.%—albumin 1.8 g., globulin 5.4 g.; alkaline phosphatase, 21 units per 100 ml.; thymol turbidity, 38 units per 100 ml.; indirect van den Bergh, 1 mg. bilirubin per 100 ml. Sigmoidoscopy showed the presence of much mucus and a thick granular mucous membrane with small bleeding areas to within 1 in. (2.5 cm.) of the anus.

Treatment.—Blood transfusion was given to improve the anaemia, but the general condition of the patient remained poor, and diarrhoea continued unchecked with ten to twelve watery stools daily. Ileostomy was performed on September 21, and when the abdomen was opened the presence of cirrhosis of the liver was confirmed. After operation her condition continued to deteriorate, and she developed abdominal pain and distension with a progressively deepening jaundice. Death occurred on October 3.

Post-mortem Findings

The body was that of a thin woman and showed a moderate degree of oedema of the ankles and clubbing of the fingers. The total length of the colon was reduced, and the wall was thick, rigid, and friable. There were firm adhesions between the ascending and descending colon and the posterior abdominal wall. The mucosa showed superficial ulceration extending from the caecum to the upper part of the rectum. Mostly the ulcers were small and were separated by areas of hypertrophic mucous membrane. There was a recent *Bact. coli* peritonitis, which was considered to be the cause of death.

The liver weighed 1,270 g. and had a finely granular surface with some larger nodules. The cut surface showed strands of white fibrous tissue running through the liver substance and destroying the normal architecture and surrounding irregular groups of liver tissue. The gall-bladder and bile ducts were normal. The spleen was enlarged and weighed 450 g. It was firm and rubbery and the pulp was deeply congested. The portal vein and its tributaries were normal. The lungs showed emphysema with congestion and areas of collapse in the lower lobes. The pleural cavities, heart, and pericardium were normal. The kidneys were normal apart from a few small areas of an early pyelonephritis.

Histology.—Liver:—There was a fine cirrhosis of the portal type. Practically all the remaining liver cells showed well-

marked fatty degeneration and there was well-marked necrosis of the liver cells in the central areas of the lobules. There was little regeneration of the liver cells, but proliferation of the bile ducts was well marked. Congestion was not pronounced and infiltration by inflammatory cells was minimal. Bile thrombi were not seen. *Colon*:—The submucosa was thickened and oedematous, and was infiltrated with lymphocytes and polymorphs. The mucosa was shed in places.

Case 3

A married woman aged 33 had a 10½-years history of diarrhoea with blood and mucus; motions numbered 14 to 20 daily in bad attacks, which were fairly well controlled by sulphonamides. She became worse in February, 1949, since when she has had fluctuating jaundice.

On examination her nutrition was fair, the conjunctivae were slightly icteric, and the fingers were clubbed. Oedema of legs and ascites were not present. Her liver was enlarged a hand's breadth below the costal margin, extending right across the epigastrium; the lower border was firm and quite regular.

Investigations.—Hb, 86%; red cells, 4,020,000 per c.mm.; white cells, 7,400; normal differential count. Urine: bilirubin +, urobilin increased. Prothrombin index, 70%; alkaline phosphatase, 13.4 units; thymol turbidity, 15 units. Plasma proteins, 8.92 g.%—albumin 3.65 g., globulin 5.27 g.%. Sigmoidoscopy showed thickening of the rectal mucous membrane with ulceration and haemorrhage. The patient subsequently improved; the jaundice has subsided, and the liver has diminished in size.

Summary

Three cases of chronic ulcerative colitis which were associated with severe liver damage are described, together with the post-mortem findings in one.

The possibility that there is a causal association between the two conditions is discussed.

I am grateful to Dr. C. C. Beatty, Dr. H. J. Orr-Ewing, Dr. D. H. Davies, and Mr. W. M. Capper for allowing me to report these cases. Dr. G. S. Andrewes kindly supplied the post-mortem and histological findings in the second case.

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Dr. L. B. Kalinowsky, addressing the Convention of the American Psychiatric Association in Detroit, put forward the view that the likelihood of obtaining a pension initiates and perpetuates many war neuroses. If the pensions were ended, he said, the neuroses would end with them. In his address, reported in the magazine *Time*, Dr. Kalinowsky said of the defeated German armies in Russia in the winter of 1942 to 1943: "Many soldiers were unable to continue due to physical exhaustion, but hysterical symptoms were extremely rare. They did not promise any gain, and failure to stay with the group could lead only to death from exposure, or, at the best, to imprisonment by the Russians." Delayed reactions when the soldier was safe were more common but usually did not last long, again because there was nothing to gain. He pointed out that in the heaviest bombing in Britain the effects on the mental health of civilians were negligible—there was nowhere for them to escape to. In the United States Army mental misfits might be expected to have been excluded on joining, but 49% of all disability discharges from the Army were on psychiatric grounds; medical rejections on such grounds accounted for 38% of all recruits. In 1926 it was decided by German psychiatrists that pensions were a factor in prolonging neuroses from the first world war, and thereafter many of the pensioners received no further help.

Medical Memoranda

Vitamin B_{12} (from Streptomyces Griseus) in Pernicious Anaemia

Vitamin B_{12}, first isolated in crystalline form from liver extracts in England by Smith and Parker (1948) and in America by Rickes *et al.* (1948a), has been shown to be effective in the treatment of macrocytic anaemias and in the prevention of subacute combined degeneration.

From the analogy that many organisms provide riboflavin for themselves, it was considered that some organisms might produce B_{12}. This was found to be the case, and the most important source so far discovered has been from various strains of streptomyces. Rickes *et al.* (1948b) obtained a crystalline material from *Streptomyces griseus*. Glaxo Laboratories have prepared concentrates from the metabolism fluid of a strain of *Str. griseus*, and it is this material that I have used on two untreated cases of pernicious anaemia. The appended results show the excellent response in each case.

CASE REPORTS

Case 1.—A married woman aged 65 complained of lassitude and a mild intermittent diarrhoea. Apart from pallor and glossitis there were no positive clinical signs. A blood count showed: red cells, 1,200,000; Hb, 29%; colour index, 1.2; reticulocytes 2.2%; white cells, 4,100, with relative lymphocytosis. Fractional test meals revealed a histamine-fast achlorhydria. The faeces contained no occult blood, and a barium enema was normal. A sternal puncture revealed a typical megaloblastic marrow. On July 1, 3 ml. of the B_{12} concentrate was given; the response is shown below.

Date	Red Cells	Hb	Reticulocytes
June 30	1,200,000	29%	2·2%
July 1 Injection			
„ 4			4·8%
„ 5			6·0%
„ 6	1,350,000	33%	10·0%
„ 7			17·0%
„ 8	1,540,000	41%	16·0%
„ 9			15·0%
„ 11	1,800,000	44%	2·8%
„ 12			1·2%
„ 13	1,900,000	45%	0·5%
„ 14	2,100,000	45%	
„ 18	2,200,000	48%	
„ 25	2,300,000	60%	

The patient had no other anti-anaemic treatment during this period.

Case 2.—A married woman aged 73 complained of generalized weakness of six months' duration. There were no positive clinical signs apart from pallor and glossitis. A blood count showed: red cells, 1,600,000; Hb 37%; G.I., 1.17; C.V., 17%; M.C.V., 106 μ^3; M.C.H.C. 32.4%; platelets 90,000; white cells, 3,000 (polys 34%, staff forms 2%, lymphocytes 64%); marked anisocytosis, poikilocytosis, and polychromasia. Sternal puncture revealed megaloblastic bone marrow. A fractional test meal showed histamine-fast achlorhydria. The patient was

Date	Red Cells	Hb	Reticulocytes
June 11	1,600,000	37%	2·0%
„ 13		35%	2·2%
„ 14			5·8%
„ 15	1,300,000	37%	10·0%
„ 16			15·2%
„ 17	1,700,000	39%	10·7%
„ 18			10·5%
„ 20	2,100,000	53%	7·4%
„ 21			4·6%
„ 22			4·5%
„ 23	2,600,000	57%	3·6%
„ 25	3,100,000	67%	1·5%

given 3 ml. of the B_{12} concentrate on June 11, and during the period recorded she had no other anti-anaemic treatment.

I wish to thank Mr. J. T. Marsh, of Glaxo Laboratories, for his information about B_{12} and his great help in preparing this note; to Glaxo Laboratories Ltd. for a supply of the material; to Dr. H. Joules, of Central Middlesex Hospital, for permission to publish this note; and to Dr. Discombe and the staff of the pathological department for their help with the haematology.

M. H. PAPPWORTH, M.D., M.R.C.P.

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Congenital Heart Disease and Dissecting Aneurysm of Pulmonary Artery

The following is a report of an unusual case of congenital heart disease in which the patient was able to lead a useful life as a shepherd until he died as the result of a dissecting aneurysm of the pulmonary artery at the age of 19.

CASE REPORT

The patient was admitted to Dundee Royal Infirmary on February 24, 1949, complaining of pain in the chest and breathlessness, which had begun four hours previously. He was born a "blue baby," but after an initial struggle for survival he suffered relatively little inconvenience, apart from breathlessness on exertion. He had measles and mumps in childhood, and after leaving school became a shepherd with his father. On the night of admission he was on the hills with the sheep, when he had a sudden pain in the left side of his chest and began to cough. He coughed incessantly for some time, with the production of blood-stained sputum, and he became breathless and cyanosed. He vomited twice on the way to hospital.

There was no family history of congenital heart disease or of any other illness, and no history of rubella during the mother's pregnancy.

On examination the patient was seen to be an underdeveloped but well-nourished youth. He was deeply cyanosed and severely dyspnoeic, preferring to lie on his side as breathing was almost impossible while lying on his back. There was pronounced jugular pulsation, thickening of the lips and nostrils, and marked clubbing of the fingers and toes. There was no oedema. The pulse rate was 120, of good volume, and regular. The apex beat was palpable in the sixth left intercostal space, 5½ in. (13.9 cm.) from the mid-sternal line. The upper border of cardiac dullness was in the third left intercostal space. The right border was 2½ in. (6.3 cm.) to the right, and the left 5½ in. to the left of the mid-sternal line. There was a systolic thrill over the whole praecordium, maximal in the second left intercostal space and pulmonary area. The heart sounds were loud and harsh, with a loud systolic murmur maximal in the second left interspace and the pulmonary area, and audible at the back of the chest. The blood pressure was 145/70.

The chest was enlarged to the left; expansion was greater on the right than the left. There was impairment of percussion note at the left base. The breath sounds were bronchovesicular and air entry was diminished at the left base. Harsh inspiratory rhonchi were heard throughout the chest. The liver extended 4 in. (10 cm.) below the right costal margin. There was no ascites. The haemoglobin was 110%, and the red cells numbered 6,200,000 per c.mm.

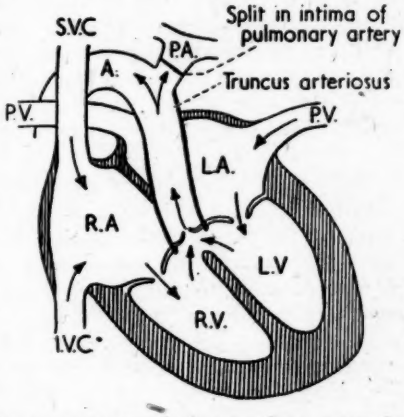
The patient received oxygen and improved a little, but he died suddenly at 6.30 a.m. the next day.

NECROPSY

The heart was grossly and symmetrically enlarged, weighing 36 oz. (1 kg.). It was globular in shape and slightly flattened antero-posteriorly. The right atrium was moderately dilated. The two ventricles and the interventricular septum were equally hypertrophied, being 2.5 cm. thick at the base of the heart. There was a common orifice centrally, immediately above the thick interventricular septum, which had three cusps, one anterior and two postero-lateral. The common truncus arteriosus was divided 2 cm. above the cusps into aorta and pulmonary artery by an antero-posterior arched beginning of the normal septum. There was thus a large arteriovenous communication.

The aorta was hypoplastic, arising from the right side of the common trunk and arching to the right, upwards, and backwards, anterior to the right bronchus. It continued downwards on the right side of the thoracic vertebrae to the diaphragm. The left subclavian and carotid arteries originated from a common trunk. On the right these vessels arose from the arch of the aorta.

There was a gross, recent, subepicardial haemorrhage over the common truncus arteriosus and the pulmonary artery as it arose from the truncus. On opening the vessels there was seen to be a circumferential tear in the media of the left lateral aspect of the pulmonary artery 1 cm. above its origin (see Diagram). A large dissecting aneurysm was present, extending from the base of the ventricles into the terminal branches of the pulmonary artery, with a false subadventitial passage which admitted a little finger. The aorta and pulmonary artery were of the same diameter and thickness. The branches of the pulmonary artery in the lungs were much larger than normal. The myocardium and coronary arteries were healthy although hypertrophied.



The left lung was very small, as it was compressed by the heart, which lay mainly in the left hemithorax. The hilum was densely infiltrated by blood from the dissecting aneurysm of the pulmonary artery, and this had extended in places to the pleural surfaces mainly in the lower lobe. On section, both lungs showed perivascular haemorrhages in the lung substance.

The liver, kidneys, and spleen demonstrated chronic venous congestion. There was also a diaphragmatic occlusion of the pylorus, with a 2–3 mm. central aperture.

COMMENT

Although cases of congenital heart disease with a persistent truncus arteriosus are not uncommon, there seem to be few recorded cases in which the patient had lived to late adolescence and had been able to engage in an occupation requiring a certain degree of stamina.

There appears to be no other recorded case of death occurring in congenital heart disease due to a dissecting aneurysm of the pulmonary artery, and this must indeed be an unusual phenomenon. The factors determining the site and time of onset of the rupture of the endothelium of the pulmonary artery must remain the subject for conjecture.

The presence of three cusps to the common truncus, and the fact that the pulmonary artery branched off the common trunk, would seem to classify this case as type 4 of Humphreys (1932).

I am indebted to Dr. J. Gordon Clark for permission to publish this case, and to Dr. H. G. Morgan for the necropsy report.

Diagram by Miss Sylvia Treadgold.

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Reviews

VISION

Recent Advances in the Physiology of Vision. By H. Hartridge, M.R.C.P., F.R.S. (Pp. 401; 236 illustrations. £1 5s.) London: J. and A. Churchill. 1950.

There can be no question of the value of the "Recent Advances" series and the usefulness of assessing recent acquisitions to knowledge in a subject such as the physiology of vision, in which experimental researches are published in many journals not regularly available to the average medical reader. Professor Hartridge's book fulfils a valuable function in this respect, for in its seventy sections vision is considered from its physical, physiological, and perceptual aspects. The book discusses in clear and simple terms a wide range of cognate problems—the nature of light and quantum mechanics, the optical properties of the eye, the photochemical and electrophysiological phenomena associated with vision, the central nervous mechanism of vision, and the perceptual appreciation of light, colour, shape, and size.

With its concise and didactic style the book provides an excellent résumé of recent experimental work on these problems, some of which (such as retinal photochemistry and the electrical responses of the retina to stimulation) are of fundamental importance. Much theory is included in the book; and this is perhaps the most vulnerable point of most books on vision. It is a subject in which it has become the habit for different investigators to build up imposing hypotheses and to seek to support them with observations some of which are subjective, many by their nature inaccurate, and most capable of more than one interpretation. The result is that many theories of questionable and equal value exist side by side. Significant advances in this complex and fascinating subject will emerge only when we begin to know more about the fundamental facts on which such a superstructure can be safely based—facts such as the minute anatomy of the recipient elements and their interrelations, the number and function of the photopigments present in the retina, and the precise variations of the electrical responses to various stimuli.

STEWART DUKE-ELDER.

THE GARDENER IN EAST AFRICA

Gardening in East Africa. Third edition. Edited by A. J. Jex-Blake, M.A., M.D.(Oxon), F.R.C.P.(London). (Pp. 399; 20 coloured plates. £1 10s.) London: Longmans, Green and Co. 1950.

It is pleasing to welcome a new edition of this most attractive and practical handbook, which first appeared in 1934 and had a second edition in 1939. Although the book is written primarily for residents of East Africa there is much in it that will appeal—and be of use—to professional and amateur gardeners in other parts of the Tropics and subtropics. All the flowers, fruits, and vegetables that have been successfully cultivated in East Africa are described, as well as many of the more attractive indigenous plants. Dr. Jex-Blake has had the assistance of several Government officials and other authorities on special groups of plants. Despite the number of contributors the volume is remarkably uniform, which is doubtless the result of a happy co-operation between the editor and his co-workers. This new edition is larger and more comprehensive than the earlier ones. Many of the chapters have been rewritten or recast, and additions made to incorporate knowledge that has accumulated in recent years. Two entirely new chapters have been added. One, intended for newcomers to East Africa, is on the oddities of East African seasons and climates; the other is on succulents, now popular as garden or rock garden plants in warm countries, especially where a dry climate prevails.

A fascinating feature of the book is the large number of beautiful coloured illustrations of many of the more decorative of the wild flowers of East Africa. Over a hundred different species are represented by twenty plates. These are mainly from Mrs. Joy Adamson's exquisite paintings of the flora of Kenya, for which she was recently awarded the Grenfell Gold Medal by the Royal Horticultural Society. The book contains much of interest about the more attractive of the wild plants of East Africa, despite the editor's lament in his preface that lack of space prevented a fuller treatment of the indigenous plants. It is refreshing to observe this interest in the cultivation of the wild plants of the country, for in the younger countries they have too often been completely neglected horticulturally.

F. N. HOWES.

MEDICAL DISORDERS OF BONES

The Parathyroid Glands and Metabolic Bone Disease. By Fuller Albright, A.B., M.D., and Edward C. Reifenstein, jun., M.D., F.A.C.P. Selected Studies. (Pp. 393; 157 figures. £2 4s.) London: Baillière, Tindall and Cox. 1948.

Few clinicians can think clearly in biochemical terms—in many branches of medicine it is not necessary for them to do so—but for understanding the affections of bones resulting from disordered general metabolism such an outlook is essential. A good test of a clinician's ability to apply his biochemical knowledge effectively is his establishment of a diagnosis of hyperparathyroidism in a suspected case. Many less rare diseases confuse the picture: myelomatosis may present as a general rarefaction of bone with a high serum calcium, and may thus lead to useless and time-consuming estimations of the calcium balance; the disease called polyostotic fibrous dysplasia has led to particular confusion, and more than half the reported cases of this condition, which is not a metabolic disorder at all, have been subjected to fruitless and unnecessary exploration of their parathyroid glands. Such errors arise from too great reliance on radiological appearances and too little on the biochemical abnormalities. They can be avoided only by an understanding of the underlying biochemical principles of metabolic bone disease.

On these basic principles, and on the clinical phenomena related to them, no authors are better qualified to write than Professor Albright and his colleagues, who have been studying these problems for more than twenty years. They have published many papers on bone diseases, and now bring all these and other unpublished experiences together in an excellently produced book. Much investigative work, with the authors' outstanding ability to mould accumulated facts into consistent working hypotheses, has made possible an unusual monograph covering most metabolic disturbances affecting bone.

A scientific argument is steadily developed throughout the book. Theories of bone metabolism in health, and of its derangement in disease, are critically considered as they affect conditions such as hypo- and hyperparathyroidism, the osteomalacias, the various types of osteoporosis, Paget's disease, and fibrous dysplasia. The clinical diagnosis and treatment of these diseases are thoroughly discussed with the authority of experience. Those who are already familiar with the writings of Albright and his school will find them conveniently collected and welded

into a coherent whole. Those who are not will find a lively, stimulating, and instructive guide to the intricacies of bone disorders encountered in clinical medicine.

This is not a complete textbook : although more than fifty pages are allotted to adult osteomalacia, rickets in children is scarcely mentioned. But the omissions are not detractions. The intention is to emphasize general principles rather than to amass uncoordinated clinical facts, and in this aim the book succeeds admirably. The reader who absorbs these principles will be enabled to apply them with success to the unusual and atypical cases he may encounter.

The book should be read by all interested in medical affections of bone as a companion to the more formal textbooks and reviews. The style is lucid and easy, the many illustrations are excellent, and frequent diagrams clarify the more complicated concepts. A full bibliography and subject index occupy the last 80 pages.

C. L. COPE.

MAN'S ABILITIES

Human Ability. By C. Spearman, Ph.D., LL.D., and Ll. Wynn Jones, M.A., Ph.D. (Pp. 198. 16s.) London: Macmillan and Co. 1950.

The late Professor Spearman is widely remembered as a pioneer of statistical method in psychology and as the originator of the celebrated "two-factor" theory of intelligence. The present book (written in collaboration with his sometime colleague and disciple, Professor Wynn Jones) is in part a restatement and in part a development of the arguments presented in an earlier book, *The Abilities of Man* (1927). In addition, it contains useful summaries of much recent work in factorial psychology and embodies a thoughtful revision of the theoretical position of its senior author. In particular, Professor Spearman shows himself well aware of the challenge to his theory which has arisen in recent years through the use of alternative methods of factorial analysis. Thus he now regards the existence of *g* (the general factor in intelligence) as a matter of statistical convenience rather than scientific fact, and modestly comments that its ultimate explanation is still "anybody's guess." This very proper caution should be well noted by all who aspire to attach psychological significance to the abstractions of statistical analysis.

This book will interest mainly the professional psychologist and others concerned with factorial analysis in a technical capacity. Although these techniques have undoubted validity and usefulness, the interpretation of factors in psychological terms is so equivocal a proceeding that any theories based upon their use must be viewed with suspicion. The book cannot therefore be recommended to the non-technical reader as an authoritative work upon its subject. None the less, Professor Wynn Jones deserves warm congratulations upon the skill with which he has edited Spearman's manuscript and upon the notable contribution which he has himself made to the argument of the book. It will remain as a worthy memorial to a forceful, distinguished, and influential contributor to the growth of psychological science.

O. L. ZANGWILL.

The third edition of *Practical Orthoptics in the Treatment of Squint*, by T. Keith Lyle, C.B.E., M.R.C.P., F.R.C.S., and Sylvia Jackson, S.R.N., D.B.O., with the assistance of Lorna Billinghurst, D.B.O., and Diana Salsbury, D.B.O. (pp. 271; 151 illustrations; £1 15s.; London: H. K. Lewis and Co.; 1949), is admirably presented; its subject is important and interesting, and the authors are to be congratulated on their powers of lucid description. Most of the pioneer work of practical orthoptics in the treatment of squint has been done in England, so it is fitting that this authoritative book should present the original work and the current teaching of practical orthoptics in this country.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Recent Advances in Chemotherapy. By G. M. Findlay, C.B.E., Sc.D., F.R.C.P. Vol. 1, 3rd ed. (Pp. 625. 36s.) London: Churchill. 1950.

The Hinge Graft, or Ginglymus Implant. By A. K. Henry, M.Ch., F.R.C.S.I. (Pp. 64. 15s.) Edinburgh: Livingstone. 1950.

Microscopic Staining Techniques, No. 2. Edited by E. Gurr, F.R.I.C., F.R.M.S. (Pp. 62. 3s. 6d.) London: Edward Gurr. 1950.

Exploring the Unconscious. By G. Groddeck, M.D. (Pp. 224. 12s. 6d.) London: Vision. 1950.

The Book of the It. By G. Groddeck, M.D. (Pp. 301. 15s.) London: Vision. 1950.

Aids to Histology. By G. H. Bourne, D.Phil., D.Sc. 5th ed. (Pp. 158. 5s.) London: Baillière, Tindall and Cox 1950.

Aids to Medical Treatment. By T. H. Crozier, M.D., D.P.H., and five contributors. 2nd ed. (Pp. 439. 7s. 6d.) London: Baillière, Tindall and Cox. 1950.

Thrombosis in Arteriosclerosis of the Lower Extremities. By E. A. Edwards, M.D., F.A.C.S. (Pp. 74. 15s.) Oxford: Blackwell Scientific Publications. 1950.

Occupational Therapy. Principles and Practice. Edited by W. R. Dunton, jun., M.D., and S. Licht, M.D. (Pp. 321. 45s.) Oxford: Blackwell Scientific Publications. 1950

Practical Neurological Diagnosis. By R. G. Spurling, M.D. 4th ed. (Pp. 268. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1950.

Major Symptoms in Clinical Medicine. By J. Almeyda, M.R.C.P., D.P.H. Foreword by Sir A. Abrahams, O.B.E., M.D., F.R.C.P. Vol. 1. (Pp. 378. 25s.) London: Henry Kimpton. 1950.

Elementary Bacteriology and Immunity for Nurses. By S. Marshall, M.D., B.S. 2nd ed. (Pp. 88. 6s. 6d.) London: H. K. Lewis. 1950.

The Asthmatic Child. By G. F. Walker, D.C.H., M.R.C.P. (Pp. 19. 2s. 6d. 25s. dozen.) Bristol: John Wright. 1950.

Principles of Medical Statistics. By A. Bradford Hill, D.Sc., Ph.D. 5th ed. (Pp. 282. 10s. 6d.) London: *Lancet*. 1950.

Bridges' Food and Beverage Analyses. By M. R. Mattice, A.B., Sc.M. 3rd ed. (Pp. 412. 38s. 6d.) London: Henry Kimpton. 1950.

Urological Surgery. By A. I. Dodson, M.D., F.A.C.S., and others, 2nd ed. (Pp. 855. 95s.) London: Henry Kimpton. 1950.

Hospital Improvements. By O. Matthews. (Pp. 32. 1s. 6d.) Published by the author, 22, Harrington Gardens, London, S.W.7. 1950.

Osteology for Dissectors. By R. K. Howat, C.M., F.R.C.S. (Pp. 292. 15s.) London: Henry Kimpton. 1950.

The Prevention of Burns in the Home. By L. Colebrook, F.R.C.O.G., F.R.S. (Pp. 20. No price.) London: Fire Protection Association. 1950.

The Natural History of Bright's Disease. By G. E. M. Scott, M.B. (Pp. 62. 15s.) Melbourne: Ramsey. 1950.

Methods in Medical Research. Vol. 2. By J. H. Comroe, jun. (Pp. 361. $6.50.) Chicago: The Year Book Publishers. 1950.

Doctors Courageous. By E. H. Hume, M.D. (Pp. 297. $3.50.) New York: Harper. 1950.

The Maggid of Caro. By H. L. Gordon, M.D. (Pp. 396. No price.) New York: Pardes. 1949.

L'Ipersessualita come Fattore Degenerogeno. By M. Benvenuti. (Pp. 208. $4.) Pisa: Omnia Medica. 1950.

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SURGICAL TREATMENT OF MITRAL STENOSIS

Cardiac surgery continues to stride ahead. It began in 1873, when Callender[1] removed the first foreign body—a needle—from the heart, but perhaps the chief honour should more justly be awarded to Rehn,[2] who first successfully repaired a cardiac wound in 1897. Rehn also performed one of the earliest pericardiectomies for Pick's disease.[3] During the 1914–18 war many cardiac wounds were repaired and foreign bodies removed from the pericardium and myocardium, and it became obvious that the heart muscle was able to withstand much manipulation and suturing. Apart from life-saving repair of these cardiac wounds, the only successful form of cardiac surgery between the two world wars was pericardiectomy for constrictive pericarditis, especially as carried out by Churchill.[4] In 1935 Claud Beck[5] and in 1936 O'Shaughnessy[6] demonstrated the possibility of improving the coronary circulation in cases of ischaemic heart disease by means of suturing some vascular tissue, such as a flap of pectoral muscle or omentum, to the surface of the heart. These operations have not proved very successful, but they showed clearly that even in the presence of the most dangerous types of myocardial disease the heart could withstand direct surgical attack. The most spectacular results of cardiac surgery have undoubtedly been in congenital heart disease. These began with the successful ligation of patent ductus arteriosus by Gross and Hubbard,[7] and the mortality rate for this operation is now no more than 2–3%. In 1945 Blalock and Taussig[8] reported their successful anastomotic operation for the relief of Fallot's tetralogy and pulmonary atresia, with a mortality rate of 10–17%. In the same year came repair of coarctation of the aorta by Crafoord and Nylin.[9] The mortality rate for this operation is now 11–16%.[10 11] Despite these remarkable feats, the successful relief of congenital or acquired heart disease by direct cardiac surgery had yet to be accomplished. This was finally achieved by Brock.[12] In a paper published in this *Journal* in 1948 he demonstrated that pulmonary valvulotomy could be undertaken as an alternative to the Blalock–Taussig operation in certain cases of Fallot's tetralogy, and that this operation offered the only means of relieving tight pulmonary stenosis with closed septa and was the best way of treating pulmonary stenosis with reversed interatrial shunt. In our editorial comment[13] at that time we suggested that the next step would be to extend surgery of the heart to acquired heart disease, and it comes as no surprise that Brock has now introduced a relatively safe and effective method of performing mitral valvulotomy, a method which he and his colleagues, Dr. Charles Baker and Dr. Maurice Campbell, describe in the opening pages of this issue. Many attempts at mitral valvulotomy have been made previously, but with little success. It seems that early failures were partly due to a wrong approach through the left ventricle and partly to a wrong kind of valvulotomy. Brock's approach is through the left atrial appendix, and he favours the finger as the best instrument for splitting the commissures of the stenosed cusps. No hole is punched out, and little, if any, incompetence results. Earlier this year Glover, O'Neill, and Bailey[14] described a very similar operation for the relief of mitral stenosis which they call commissurotomy. They reported eight cases with three deaths, and mentioned an additional 22 cases with three more deaths since their paper was submitted for publication. Baker, Brock, and Campbell also report eight cases in detail and mention one more in an addendum—giving a total of nine cases with two deaths. The results in the successful cases have been gratifying.

The type of case specially selected for valvulotomy so far has been characterized by tight mitral stenosis with relatively little incompetence, secondary pulmonary hypertension, a powerful right ventricle, and symptomatically by attacks of paroxysmal cardiac dyspnoea. The cardiac output is strictly limited and rises but little on effort. Pulmonary congestion is intense and causes reflex dyspnoea. It is known that about 10% of all cases of mitral stenosis take this course, and that mitral stenosis accounts for about 10% of all cases of organic heart disease. It follows that approximately 1% of all cases of heart disease should benefit by mitral valvulotomy. At present congenital heart disease accounts for 2% of the organic cardiopathies, and operative treatment is practicable in about half of the patients so afflicted. It follows that mitral valvulotomy is likely to be undertaken as frequently as all the operations for congenital heart disease put together. The success and

[1] *Med.-chir. Trans.*, 1873, **56**, 203.
[2] *Arch. klin. Chir.*, 1897, **55**, 313.
[3] *Berl. klin. Wschr.*, 1913, **50**, 241.
[4] *Ann. Surg.*, 1936, **104**, 516.
[5] Ibid., 1935, **102**, 801.
[6] *Brit. J. Surg.*, 1936, **23**, 665.
[7] *J. Amer. med. Ass.*, 1939, **112**, 729.
[8] Ibid., 1945, **128**, 189.
[9] *J. thorac. Surg.*, 1945, **14**, 347.
[10] Shapiro, M. J., *Amer. Heart J.*, 1949, **37**, 1045.
[11] Gross, R. E., *Circulation*, 1950, **1**, 41.
[12] *British Medical Journal*, 1948, **1**, 1121.
[13] Ibid., 1948, **1**, 1192.
[14] *Circulation*, 1950, **1**, 329.
[15] *J. Amer. med. Ass.*, 1949, **140**, 1259.
[16] Wood, P., *Proc. R. Soc. Med.*, 1949, **43**, 195.

the relatively low mortality that have attended mitral valvulotomy are likely to encourage thoracic surgeons to prefer the direct attack to the anastomotic operation of Bland and Sweet,[15] which requires no less skill to perform and which relieves pulmonary congestion only at the expense of interfering with the compensatory mechanism for maintaining an adequate blood flow through the mitral valve.

It remains to be seen at what stage in the development of mitral stenosis operative interference should be advised and how long the improvement lasts. Physicians can no longer disregard significant mitral incompetence, and there must be a general tightening up of the precise functional and anatomical diagnosis of established mitral-valve disease. Significant incompetence is recognized by the combination of a loud mitral systolic murmur, often accompanied by a thrill, left ventricular enlargement, and conspicuous paradoxical pulsation of the left auricle.[16] At the present time recommendations for valvulotomy might be based on the following criteria: no demonstrable rheumatic activity nor likelihood of further activity; the presence of tight mitral stenosis with little incompetence and uncomplicated by significant aortic or tricuspid-valve disease; relatively slight enlargement of the left auricle; radiological evidence of pulmonary venous congestion; a mean pulmonary artery pressure of at least 30 mm. of mercury; an electrocardiogram showing right ventricular dominance in multiple V chest leads; and serious incapacity caused by breathlessness on effort. If patients could be selected at this stage rather than after the development of paroxysmal cardiac dyspnoea many lives should be saved. Already patients have died from pulmonary oedema while waiting admission to hospital for valvulotomy. Auricular fibrillation and fluoroscopic evidence of mitral-valve calcification are not necessarily contraindications to valvulotomy, but the risk of embolism is probably greater in these cases.

SECURITY AND INCENTIVE

Many doctors to-day have some familiarity with English social history and with the great influence of social agencies upon medical progress, but the history of Scottish social welfare is less well known. Professor Thomas Ferguson[1] has recently met the need for an account of the development of social services in Scotland in a book which is concerned largely with subjects of medical interest, such as the control of infectious disease, the relief of destitution, the improvement of environmental hygiene, and the provision of medical care. The narrative begins with mediaeval times and ends with the appointment of the first medical officers of health in Scotland in the years 1862–3. In many respects this account is consistent with the more familiar English social history, though conditions in Scotland were if anything worse than in England. Chadwick wrote in 1842: "It might admit of dispute, but on the whole it appeared to us that both the structural arrangements and the condition of the population in Glasgow were the worst of any we had seen in any part of Great Britain." Ferguson's description of the growth of social welfare may remind the reader that security and incentive are merely new terms for an old problem—how to relieve distress without encouraging idleness. This question touched the conscience of society at two points, and the spirit of early social welfare in England was in consequence severe by modern standards. Scottish benefactors were certainly not less alive to their moral duty; they operated on the principle that "no person should be maintained by charity in the same manner that he lived by labour: there ought not only to be a descent from station, but an abridgement of comfort, and the object ought never to be more than a mere decent subsistence." This view persisted during the nineteenth century: to the sweet of its charity Victorian philanthropy still added the bitter of its castigation.

It is not easy to account for the profound change in attitude during the last hundred years, which has led to replacement of charity by social security and to consideration of incentives and human relations in preference to penalties for social failure. One factor was undoubtedly the creation by the industrial revolution of a large group of able-bodied individuals who were impoverished not because they were unwilling or unable to meet the demands of society but because society no longer made demands on them. The view that poverty could be regarded as a fair penalty for failure to provide for oneself became plainly untenable in an age of rapid industrial development. Ferguson quotes a remark of Lord Cockburn: "Of all the new features of modern society, none is so peculiar or so frightful as the hordes of strong poor, always liable to be thrown out of employment by stagnation of trade. There have been above ten thousand of them in Paisley alone for more than a year and a similar cloud darkens every considerable town in Scotland." The new class became an important one when it discovered that "their number was their force," and by the end of the century Simon wrote of "very promising progress in the art of confederating for common interest."[2]

The modern attitude to social welfare has also been influenced by the work of the geneticist. Lancelot Hogben[3] observed that the eighteenth-century humanitarians were under no illusions about the meaning of equality and would have been less

[1] *The Dawn of Scottish Social Welfare*, 1948, London.
[2] *English Sanitary Institutions*, 1890, London.
[3] *Genetic Principles in Medical and Social Science*, 1931, London.

discomfited by the results of modern genetics than biologists of the generation which followed them. Rousseau, in particular, was quite clear on this matter. He wrote: "I conceive that there are two kinds of inequality among the human species: one, which I call natural or physical, because it is established by nature and consists in a difference of age, health, bodily strength, and the qualities of the mind or soul; and another, which may be called moral or political inequality, because it depends on a kind of convention and is established or at least authorized by the consent of men." But so long as the view that human beings were equipped equally at birth was contradicted by no substantial scientific evidence, society had not on its conscience the possibility that environmental handicaps were commonly added to constitutional ones. This source of comfort has been taken from us, and no statesman to-day, at least no Western statesman, is likely to dedicate a nation to the proposition that men are created equal. Moreover, the fact of human inequality has been settled beyond reasonable doubt at a time when we face squarely the practical implications of the doctrine of human rights. While large numbers of the population were still illiterate the principle of social justice was in the nature of a blueprint for the shape of things to come. In consequence of the progressive development of social and political institutions in the West it has become necessary to implement the good intentions of our predecessors by equating ability and opportunity. It will not be easy. And this immense undertaking is further complicated by the fact that the world's work is very unequal in its demands and satisfactions; taking from each according to his ability may be quite incompatible with giving to each according to his need.

It is at least something that the nature of the problem is now clear: a society irrevocably opposed to selective breeding must contrive to get the world's work done by individuals possessed of equal rights and unequal gifts.

MULTIPLE HAEMAGGLUTININS

A few months ago attention was directed to the importance, both medical and scientific, of the haemagglutinins recently discovered in the sera of patients, mostly after multiple transfusions.[1] In the majority of cases these antibodies were found singly, accompanied only by the naturally occurring agglutinins appropriate to the patient's ABO blood group. The number of known antibodies is now so great, and such large numbers of sera are being tested, that through the mere operation of chance sera will inevitably be found from time to time containing two, or even three, different antibodies. This possibility must always be borne in mind in the investigation of a case of haemolytic disease of the newborn or of a transfusion reaction, and even in the routine tests carried out before an apparently straightforward transfusion. Apart from the combination of anti-C + anti-D, which is nearly as common as pure anti-D and commoner than pure anti-C, a number of sera have been described containing two abnormal antibodies, such sera including most examples of those containing anti-S. When, however, four or more abnormal antibodies are found in a single serum the suspicion must arise that their concurrence is not due solely to chance but that the patient has a congenital predisposition to make unusual antibodies in response to stimuli which fail to affect most other persons. The existence of such a predisposition was clearly demonstrated in one case by Callender and Race,[1] since the patient, in response to a succession of transfusions in a period of a few months, was observed to make five rare antibodies, three of them being hitherto unknown, and in most cases the relationship between the stimulus and the response was precisely observed.

In this issue of the *Journal* two cases are described in which multiple abnormal haemagglutinins were found in the serum after the patients concerned had had several blood transfusions. Dr. R. H. Malone and Mr. J. Cowen found the rare antibodies anti-E and anti-M, both active at 37° C., and the cold agglutinin anti-P, all appearing for the first time within a period of one month during a series of blood transfusions. There can be little doubt that in this patient their development was due to a special faculty for making antibodies in response to transfusion. In the case described by Drs. J. O. Collins, R. Sanger, F. H. Allen, and R. R. Race, in addition to anti-A and anti-B, seven abnormal antibodies, mostly of very rare types (five of them active at 37° C.), were found together in the serum of a patient who had received numerous transfusions. Here there can be no question whatever of coincidence, though the precise times of development of the antibodies are not known. The thermal range of the antibodies is relevant to the question of immunization, since in general immune agglutinins are more active at body temperature and naturally occurring ones more active in the cold.

The immediate task when cases of this kind are found is to select suitable blood for transfusion and to avoid further sensitization of the patient. Persons with multiple antibodies are, however, so rare that this urgent practical problem, though closely affecting the individual patient, is of little general importance. Moreover, the mere investigation of mixed antisera so as to identify the individual antibodies, though it calls for the resources of a specialized laboratory and for great skill in serology, can become a mere academic exercise if the antibodies to be found are all of known types. The scientific value

[1] *British Medical Journal*, 1950, 1, 592.
[2] *Ann. Eugen., Lond.*, 1946, 13, 103.

of these investigations appears only when all the known antibodies present in a serum have been identified and a search begins for unknown types. The work described in the two papers in this issue was clearly directed towards this end, but the authors were unfortunate in not finding any new antibodies. Such research, however, has its rewards, as was shown by Callender and Race when they found three new antibodies in the serum of one patient. Investigation of such cases may also throw light on the mechanism of antibody formation. The patients concerned have suffered from a variety of chronic diseases, each calling for multiple transfusions, but when more such cases have been collected, as they undoubtedly will be, a particular disease or class of diseases may clearly prove to be the usual accompaniment of multiple immunization to blood-group antigens. Physiological and pathological investigation of the patients may then supply new knowledge about the mechanism of immunity and thus lead to further advances in the prevention and cure of infectious diseases and of haemolytic disease of the newborn.

ANOTHER ANTIBIOTIC SUBSTANCE

Terramycin is a new antibiotic drug isolated by Finlay and his colleagues from *Streptomyces rimosus*,[1] and workers at the Mayo Clinic have now given a full account of its pharmacology and some information about its action in human and experimental infections.[2] Terramycin can be estimated by its inhibitory action on the same strain of *Bacillus cereus* as is used for the assay of aureomycin. It is readily absorbed after oral administration in man, and single doses as large as 3 g. have been given. Detectable amounts of the substance have been found in serum 24–26 hours after administration, though the concentration begins to decrease after six hours. Terramycin, like penicillin, streptomycin, and aureomycin, passes the placental barrier and reaches the foetal circulation. It diffuses into pleural fluid, and its presence can be demonstrated in bile and urine after being given by mouth: roughly speaking, the higher the level in the serum the greater the concentration of terramycin in the urine. Large amounts of the substance are unabsorbed and excreted in the faeces. The bacterial flora is completely changed, as Dearing and Heilman[3] also found after the administration of aureomycin. The faeces become odourless, and coliform organisms, streptococci, and clostridia disappear; yeasts, micrococci, and *Candida albicans* alone remain. The close similarity between terramycin and aureomycin is further emphasized by Welch and his colleagues.[4] Infra-red spectrum analysis shows that although there are definite differences in molecular structure the "finger-print" analysis has many points of similarity. Terramycin is more active than aureomycin against certain strains of organism, but with other strains of the same species the reverse is true. With both drugs serum concentrations are similar after comparable single doses, and increasing the dose of either drug beyond 1 g. does not materially increase the blood concentration. Both drugs cause some looseness of the stools, but this is not surprising with any drug which greatly changes the intestinal flora. Terramycin is excreted in the urine to a greater extent than aureomycin. Terramycin has as wide a bacterial spectrum as aureomycin, attacking both Gram-positive and Gram-negative bacteria. It is especially active against clostridia and saprophytic mycobacteria, but has little or no action on fungi. Brucellae are inhibited by from 0.2 to 0.4 μg. per ml. of medium. In mice infected with *Brucella suis* the suppressive action of 0.5% of terramycin hydrochloride in the diet is considerable, but, like aureomycin, terramycin does not eliminate all organisms from the spleens of infected animals, and its effectiveness is much increased by combination with dihydrostreptomycin. The Lansing strain of poliomyelitis in mice is unaffected by the drug.

Terramycin has so far been given to man only by mouth. Doses of 1 to 1.25 g. every six hours are adequate: this represents roughly 4–5 g. daily for the average adult. Gastro-intestinal irritation with nausea and vomiting may occur, but is less than with aureomycin: it can be controlled by giving the capsules with milk, which does not interfere with the absorption of terramycin. The Mayo Clinic workers give details of 12 patients treated with this antibiotic. A patient with acute laryngotracheitis due to *Haemophilus influenzae* recovered after receiving 12 g. in three days. Two patients with pneumonia were treated for seven days with daily doses of 4 g. Septicaemia (one case), urinary infection due to *Bacterium coli* (two cases), and streptococcal tonsillitis (two cases) were promptly relieved. A patient critically ill with a *Bacteroides* septicaemia was treated for 13 days with 5 g. daily, followed by 4 g. for a further seven days: temperature fell after seven days' treatment. Herpes zoster (one case) was unaffected, but one patient with severe erythema multiforme improved after administration of the drug.

DIMETHYL ETHER OF TUBOCURARINE

The dimethyl ether of tubocurarine, described by King in 1935, has been found to be much more potent in relaxing the skeletal muscle of animals than tubocurarine, though the relative potency of the two substances varies in different species: except in the mouse the dimethyl ether is from 2 to 10 times as potent as tubocurarine. Elsewhere in this issue Dr. H. O. J. Collier and Mr. R. A. Hall describe the results of their pharmacological investigation of this substance. They found in the first place that its paralytic effect is antagonized at least as well by neostigmine as is that of tubocurarine. They next studied the effect on the blood pressure. Tubocurarine brings about a fall in two ways: it diminishes the flow of impulses through sympathetic ganglia, and it releases histamine in the blood. The evidence indicates that the dimethyl ether is not more active than tubocurarine in exerting these effects, so that the extra potency of the dimethyl ether is not offset by an increase in side actions. Thus it appears that the dimethyl ether has some advantage over tubocurarine for clinical use. In a paper also published in this issue Drs. H. B. Wilson, H. E. Gordon, and A. W. Raffan describe results obtained with the dimethyl ether of

[1] *Science*, 1950, **111**, 85.
[2] Herrell, W. E., Heilman, F. R., Wellman, W. E., and Bartholomew, L. G., *Proc. Mayo Clin.*, 1950, **25**, 183.
[3] Ibid., 1950, **25**, 87.

D-tubocurarine in 100 thoracic operations. They found that this drug was 2 to 2½ times more potent than D-tubocurarine chloride, that the duration of its action on diaphragmatic activity was rather shorter, and that there seemed to be less release of histamine as judged by the maintenance of systolic and diastolic blood pressure. They had previously noted that with tubocurarine it is sometimes difficult to inflate a collapsed lobe of lung, and they consider that this may be due to the constriction of bronchioles by the histamine release. With the dimethyl ether they found no difficulty in inflating a lung or a lobe which had been allowed to collapse. The evidence suggests that the introduction of the dimethyl ether of D-tubocurarine may be a modest but definite advance.

SURGICAL RELIEF OF MENTAL ILLNESS

Those who have felt concerned about the increasing popularity of neurosurgical operations for relief of chronic mental illness have long been demanding a more thorough and detailed investigation of their after-effects. The award of the Nobel Prize to the originator of our present methods fortunately coincided with the publication of a study in the U.S.A. which should satisfy some of these demands.[1] In this investigation control cases lived in the same hospital conditions and were subjected to the same "total push" and multiple testings as those who had the operation. Forty-three investigators went to work with great intensity on 48 patients, 24 of whom had various areas of frontal cortex removed at open operation, while the controls were given the preliminary anaesthetic. Findings have been reported in five hundred pages of biochemical, electro-physiological, neurological, neurosurgical, psychological, and psychiatric data. Some may still remain uneasy because of the paucity of positive new information afforded by the investigation, but it does confirm much that is already claimed by previous workers. For instance, 35 different psychological tests were given before and after operation, from which 135 scores of performances were derived. When sufficient time had elapsed after operation, "in nine out of ten tests neither the average nor the variability of the operated group differed significantly from that of the control group." The important positive finding was a decrease of painful self-consciousness and anxiety and a shift of complaints, real or imaginary, from the centre to the periphery of thought.

The patients operated on had various areas of cortex removed by an open operation, so as to make more certain what parts of the frontal lobe actually sustained damage. The best clinical results followed when the rostral part of area 9 and caudal part of area 10 (Brodman) were removed. Patients ill over 20 years were among those who recovered and were able to do satisfactory work. This suggestive finding, however, must be considered in conjunction with the fact that the extent of the damage as well as the site is known to be of great importance. The results are obviously a great improvement over those obtained when well-preserved patients are subjected to more posterior "standard" leucotomy operations. Equally good results have, however, been obtained in England and elsewhere when forward undercutting of the frontal cortex has been attempted rather than its removal. Undercutting is likely to prove the more practical procedure for the general run of patients. This work again demonstrates that psychiatric patients can undoubtedly survive operations on the frontal lobes which relieve intolerable mental tension and leave intellectual abilities relatively intact. They can also retain an efficient working capacity. But the extension of the use of leucotomy to the better-preserved patient is going to require increasing co-operation between the neurosurgeon and the psychiatrist.

[1] *Problems of the Human Brain. Selective Partial Ablation of the Frontal Cortex*, by the Columbia-Greystone Associates and edited by Fred A. Mettler, 1949, New York.

PYELONEPHRITIS AND PARASYMPATHOMIMETIC DRUGS

Parasympathomimetic drugs may be divided into three main groups: the older alkaloids, pilocarpine and muscarine, which are now seldom used in therapeutics; the inhibitors of cholinesterase—physostigmine and neostigmine, the former being used mostly in ophthalmology to contract the pupil and the latter for its effects in myasthenia gravis; and substances which act like acetylcholine but which can be used in therapeutics because of their greater stability—acetyl-β-methylcholine ("mecholin" or "mecholyl") and carbachol. Mecholyl is used to a limited extent for the control of supraventricular paroxysmal tachycardia and carbachol occasionally for the relief of intestinal ileus and for its vasodilator effect in Raynaud's disease and intermittent claudication. Its main value in therapeutics, however, is to empty the bladder in the urinary retention which may occur after surgical operations or lesions of the spinal cord. Drugs like carbachol sometimes have alarming toxic effects and should not be given to gravely ill, collapsed, or very elderly patients. Among these ill-effects are headache, sweating, nausea, colic, involuntary defaecation, substernal discomfort due to bronchospasm or cardiospasm, and flushing and faintness due to a precipitate fall in blood pressure: most may be antagonized by atropine. A few fatalities have been reported after the use of mecholyl and carbachol, usually due to accidental overdosage or to the drug having been administered by error intravenously. Recently Ney and Horowitz[1] have reported a further complication resulting from the use of a new parasympathomimetic drug. The administration of "furmethide" (furfuryl trimethylammonium iodide) caused acute pyelonephritis in two patients with lack of control of micturition (and large amounts of residual urine) due to disease of the spinal cord. In the author's opinion this complication was due to a back-flow of urine up the ureter into the kidney from a bladder contracting forcibly against a urethral resistance greater than the reflux resistance. There is no reason to believe that furmethide is more liable to cause this than any other parasympathetic stimulating drug such as carbachol, which should therefore be used with caution when a large amount of infected residual urine and a possible vesico-ureteral reflux are present.

Professor Hans Selye, of Montreal, will give the Heberden Oration before the Heberden Society at B.M.A. House on Friday, June 2, at 5 p.m., and on Saturday, June 3, at 10 a.m. Professor Selye will speak on "The Rheumatic Diseases as Diseases of Adaptation."

[1] *J. Amer. med. Ass.*, 1950, **142**, 12.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

THE MANAGEMENT OF ASTHMA

BY

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Asthma is rightly included among the psychosomatic disorders. It is now widely recognized that in most cases there is an allergic basis, with secondary infection of the bronchial tree as an added factor of considerable importance. The neurotic individual who is also asthmatic may give expression to his subconscious conflicts by an increase in the frequency and severity of asthmatic attacks. It is less certain that asthma can occur solely as the result of infection or psychoneurosis in the absence of an allergic foundation, though the allergic element is often submerged by these factors and may be therapeutically of minor importance.

The principles underlying the management of asthmatic patients have not altered in recent years, though new therapeutic agents have been introduced. A careful history designed to establish the relative importance of these allergic, infective, and psychological factors is essential. It is important to recognize that the longer the duration of the asthma the more likely it is that all factors are playing their part in maintaining the asthmatic state.

Pure allergic asthma is most commonly seen in children and young adults. A family history of allergy and a personal history of associated forms of allergy are frequent. Eosinophils and Curschmann's spirals are often found in the sputum. Such patients are predisposed under suitable conditions of exposure to develop sensitivity to molecules, chiefly of a protein or protein–carbohydrate nature, including many forms of inhalants and foods, and to certain drugs which probably acquire antigenic properties as the result of conjugation with body proteins. It is therefore not surprising that most asthmatics are sensitive to a variety of agents, and that asthma due to solitary atopens (allergens) is relatively uncommon : sensitivity to grass pollens accounts for the majority of cases in which one atopen is responsible for the symptoms.

Hyde (1949) has published a chart showing the seasons during which the pollens of various anemophilous trees and plants are found in the atmosphere of Great Britain, and this should help in the diagnosis of the more unusual cases of pollen allergy. Hyde and Williams (1946) have also pointed out that Alternaria spores are present in great numbers during the latter part of the summer, and these, too, may account for some cases of seasonal allergy. Increasing attention has been paid to fungus sensitivity in recent years, and its importance in this country may be greater than was previously supposed. Sensitivity to house dust, animal hair, and to materials of animal or vegetable origin encountered at work or in the home may also be suspected from the history.

Skin Tests

Confirmation should be obtained by skin tests and by experimental exposure when this can conveniently be done, if possible without the patient's knowledge. In this country skin tests have never achieved the importance ascribed to them in the U.S.A., possibly because, owing to our climate, infection plays a relatively more important part, but also because positive skin reactions so often lack clinical confirmation. The potency of extracts put up by pharmaceutical firms varies considerably, and, except with pollen, no commercial attempt at standardization by biochemical methods has been made in this country. Most pollen extracts give reliable results when tested by the prick or scratch method. Extracts of most other atopens, including foods and inhalants, tend to give too few reactions by this method. On the other hand, intradermal tests, particularly to inhalants, give too many positive reactions and may be dangerous in inexperienced hands. Now that preparation of dust and mould extracts has been carried out in a scientific manner (Rimington *et al.*, 1947 ; Maunsell *et al.*, 1947) there is some hope that purified and standardized preparations of various allergens may become available for testing, and that scratch tests with all extracts will be as reliable as are those with grass pollen at present.

Infection should be suspected if the attack of asthma lasts for weeks or months rather than for hours or days, if there is yellow sputum, or if the patient is pyrexial ; adrenaline will be relatively ineffective in these cases. The history of an infection of the upper respiratory tract before the development of asthma is also suggestive, but it must be remembered that allergic rhinorrhoea is often mistaken for a head cold. Examination of the sputum will show pus and organisms ; typical Curschmann's spirals will be absent. Sometimes sputum cultures repeated at intervals of several weeks will show that an organism of one type persistently predominates, but more commonly organisms of low pathogenicity, which vary from time to time, are grown.

Psychological Factor

The importance of the psychological factor in asthma is now well recognized, in large part because of the work of British observers. Its relative importance is not always easy to assess, but the family doctor is in a particularly favourable position to do this. He knows the family background, the parents who are over-solicitous, the mother whose child is unwanted, and the unhappy home where the atmosphere is described as " stifling " or where anxiety lies like a " weight on the chest." In a series of severe cases of chronic asthma personally investigated an unhappy home atmosphere was surprisingly common. These patients may use their asthma as a means of obtaining sympathy, as a weapon or an excuse, as the expression of a mental conflict, or, more rarely, as a symbol which represents some childhood incident long repressed into the subconscious.

The mechanism of the conditioned reflex must also be remembered : an incident which calls to mind the circumstances in which an asthmatic attack has taken place may itself lead to the recurrence of symptoms. The adult patient should be encouraged to discuss his environment at home and at work and the stresses which lie beneath the surface, and to relate emotional incidents to attacks of asthma. In children the attitude of the mother towards the child is often obvious, and impressions can be confirmed or modified in the course of conversation ; the relations between the parents and between siblings should also be sought.

Treatment of the Allergic Factor

The allergic aspect is most easily dealt with and responds better to treatment. Suspected atopens should be avoided so far as is possible. The sorbo pillow can once more be obtained for those who are sensitive to feathers or kapok. Change of occupation or residence may sometimes be necessary, but should never be recommended without good evidence that the patient is likely to be better in a new occupation or locality; a preliminary trial period is advisable. The patient's occupation or the ubiquity of the atopen to which he is sensitive—for example, house dust—may make it impossible to avoid contact with agents to which he is sensitized: in such cases hyposensitization should be attempted by injection of increasing quantities of one or several extracts.

It is important to remember that the effect of this treatment is as a rule only temporary, and in successfully treated cases boosting doses at monthly intervals will sometimes keep the patient in good health. Even then fresh sensitizations may develop in the course of the disease. Most firms provide a suggested scale of dosage for desensitization with the extracts supplied. There is always a risk, however, that a severe general reaction may follow in very sensitive patients, especially after the first or second injection or on changing from a weak to a strong solution. This may take the form of severe urticaria, angioneurotic oedema, rhinorrhoea, asthma, and collapse. In order to avoid such an event the first dose should be gauged by the size of the skin test, and great care should be taken to ensure that the material is not accidentally injected into a vein. The addition of 3–5 min. (0.18–0.3 ml.) of adrenaline hydrochloride (1 in 1,000) to each dose of extract serves further to diminish the chances of severe reactions, but also delays their onset.

Every patient should be kept under observation for half an hour after each desensitizing injection. The symptoms of a reaction can normally be controlled by the injection of 5–10 min. (0.3–0.6 ml.) of adrenaline hydrochloride (1 in 1,000), but it may be necessary to repeat this several times before complete recovery occurs. Antihistamine drugs (50–150 mg.) may also diminish the effects of such reactions, but in severe cases they do not act quickly enough, nor are they ever as effective as adrenaline.

Treatment of Infection

Cases in which infection plays a predominant part are more resistant. This is partly because symptomatic treatment, which is discussed below, is far less effective and partly because eradication of infection from the bronchial tract is often exceedingly difficult. The remedies employed in bronchitis may be effective in the milder cases—that is, rest in bed in a constant temperature, the use of expectorants such as potassium iodide and simple alkaline mixtures, inhalation of tinct. benzoin. co., and breathing exercises designed to encourage expiration and expectoration.

In severer cases penicillin may be invaluable, and used in combination with sulphonamides can save life and will often reduce the period of invalidism by many weeks. These drugs should be given boldly, and, provided improvement takes place, they should be maintained for an adequate period of time—up to 30 g. of sulphonamide over five to seven days and full doses of penicillin for one to two weeks. The latter may conveniently be given as procaine penicillin or in the form of a stearate, 300,000 units twice daily. It may also be administered as an aerosol by means of an atomizer fitted with a mouthpiece and attached to an oxygen cylinder; in this way 20,000 units may be absorbed intrabronchially every hour during inhalation for five to ten minutes. The too frequent use of penicillin will encourage the growth of resistant organisms, and it should therefore be restricted to cases of severe asthma which have not responded to simpler measures or in which life may be in danger. Sensitivity to penicillin or sulphonamides, which may themselves cause asthma, has been recorded, and for this reason, too, they should be employed with caution. Vaccines are still used, but in my experience are seldom of value: they may be helpful when one type of organism is grown in pure culture or constantly predominates in the sputum and seems to be responsible for maintaining the infection.

Psychological Treatment

The best results of psychological treatment are often seen in children; the approach should be indirect through the parents, who must be reassured so that they avoid the appearance of anxiety in the child's presence. They should be encouraged to allow him to lead as normal a life as possible, and helped to understand and so to relieve the underlying tensions.

Encouragement and a reasonably optimistic outlook are essential in the treatment of all asthmatics, and wise advice on how to live with and control the disease should be given. When there is an obvious source of anxiety this must be faced and the patient led to appreciate the connexion between it and his attacks. Adjustment of environmental factors is sometimes possible, usually by removal of the patient to more congenial surroundings. In difficult cases expert psychiatric assistance may be valuable.

Control of Attacks

When the main aetiological factors have been dealt with the direct control of attacks must be considered. It cannot be too strongly emphasized, however, that to prescribe symptomatic remedies alone is to invite failure; asthma remedies must be intelligently used, and whenever possible should be complementary to treatment of the causal factors. In mild recurrent asthma, especially of fairly recent onset, breathing exercises are often beneficial. These must be given by a qualified instructor along the lines laid down in the booklet published originally by the Asthma Research Council.* Stress is laid on expiration and the movements of the diaphragm and lower thorax. The reason for the improvement which follows is unexplained; it may be partly psychological and partly brought about by helping the patient to expectorate mucus squeezed from the bronchioles during expiration. The best results seem to be obtained in those with mild bronchial infection.

In the same type of case with mild recurrent symptoms broncho-dilator drugs are helpful. There are now a good variety of these—ephedrine, ½ gr. (32 mg.), still retains its value and is often more efficient if combined with theophylline, 2 gr. (130 mg.), phenobarbitone, ½ gr., or "sodium amytal," 1 gr. (65 mg.). Certain synthetic adrenaline analogues (isopropyl-*nor*adrenaline) are sold under various trade names, including "neo-epinine," aleudrine," "neodrenal," and "isupren." These are prescribed in 20-mg. doses and have the advantage of being absorbed perlingually, but, like adrenaline, they often cause palpitations. I have not found them to offer any striking advantage over ephedrine, though some patients prefer them.

Antihistamine drugs are also disappointing in the treatment of asthma. Mild cases of allergic asthma may be

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controlled by regular administration three times daily : most of these drugs are prescribed in 50–100 mg. doses, but "antistin" is well tolerated in double this amount. The best results are obtained in those who are troubled by nocturnal wheezing. "Anthisan," 50–200 mg., and "phenergan," 25–75 mg., both exert their effects for at least twenty-four hours and may be given in one dose at bedtime, when the sedative side-effects which may be present are beneficial. As side-effects are relatively common, small doses must be given at first : if drowsiness develops amphetamine sulphate (5 mg.) may be used to counteract it, but in many patients the narcotic effect disappears spontaneously after a few days. It is also important to remember that after a course of treatment with maximum dosage the drug must be gradually reduced or so-called "rebound" effects occur with intensification of symptoms. Sensitization to antihistamines has been recorded, and they are of no value in severe attacks or when infection is present. It is worth remembering that the response to these drugs as regards both their anti-allergic properties and their side-effects is surprisingly individual and one may succeed where another causes only vomiting or drowsiness.

Nebulizers are widely used by asthmatic subjects in the form of small hand-sprays and of more elaborate apparatus attached to an oxygen cylinder : so long as they are employed only occasionally there is no objection to them. In severe cases, however, when they are used frequently they are certainly harmful whether they contain adrenaline hydrochloride (often employed in a concentration of 1 in 200 in 10% glycerin), adrenaline analogues, or proprietary preparations containing combinations of various antispasmodic drugs. It is not always recognized what a large quantity of these substances can be absorbed in this way.

Adrenaline still remains the chief symptomatic remedy in the severer case, and it is sometimes justifiable to teach the patient to give his own injection (2–5 min. (0.12–0.3 ml.) of 1 in 1,000 adrenaline hydrochloride) early in the attack. He must be warned against the danger of accidental intravenous injection, an error which may be followed by hemiplegia or, possibly, death. In severer attacks bigger doses can be safely given by Hurst's minim-a-minute method. Preparations of adrenaline in oil, or in the form of a mucate (hyperduric adrenaline), are sometimes useful, especially at night because of their slow absorption. In recent years aminophylline (theophylline with ethylenediamine *B.P.*) has achieved an importance second only to adrenaline and is a genuinely useful preparation. The intravenous injection of 0.24–0.5 g. may cut short severe and long-standing attacks when adrenaline in large doses has proved ineffective. A disadvantage is that it is most effective when given intravenously, and this is not always convenient. By mouth (1–3 gr.—65–200 mg.) it is of little value except as an adjuvant with other drugs ; it also is a gastric irritant.

Status Asthmaticus

Status asthmaticus still remains the bane of the physician and the patient's nightmare. In the early stages the bold use of adrenaline or aminophylline, and, if necessary, removal to hospital may arrest the condition, but the tragic patient who relapses after a short period of improvement, who is prevented from sleeping by his dyspnoea, and who becomes dehydrated and ketosed from inability to take food is always a source of anxiety. A low-grade infection is often present in these cases, and it is in them that penicilfin can produce dramatic improvement. It may be given by the usual intramuscular route or as an aerosol delivered continuously into an oxygen tent or inhaled intermittently with the aid of a nebulizer. In my experience the inhalation methods have little if any advantage over injection.

Treatment with intravenous infusions of aminophylline in a glucose-saline drip may be useful : 0.5 g. of aminophylline may be added to a litre of glucose-saline (0.4% glucose, 0.18% NaCl) and run in at the rate of 60 drops a minute. If the drip is to be maintained for twelve hours or longer the rate should be reduced by half ; a total of 3 g. of aminophylline may be given safely in twenty-four hours. Ethyl alcohol 5% in glucose-saline, with the addition of 0.3–1 ml. of adrenaline hydrochloride 1 in 1,000, has also been used and helps the exhausted patient to sleep. These remedies should be given cautiously and should not be continued if improvement is not early apparent ; adrenaline may be harmful to those who are "fast" to this drug, aminophylline can cause circulatory collapse, and with intravenous therapy there is always a risk of pulmonary oedema if bronchopneumonia is present. The rectal administration of ether in olive oil (3 oz. (85 ml.) in 5 oz. (142 ml.) of olive oil for an adult) may give much needed sleep. Paraldehyde is also useful in this respect ; it is most effective given intramuscularly in an adult dose of 2 ml., repeated if necessary after an hour.

Bronchoscopy carried out under local analgesia, with removal by suction of thick mucus obstructing the bronchi and bronchioles, may bring about dramatic improvement in resistant or apparently hopeless cases.

Morphine unfortunately is still given in asthma ; this is inexcusable because of the high death rate due to respiratory failure and because of the possibility of addiction, which is always present when this drug is used in chronic illness. Aspirin is also dangerous in asthma ; Salén and Arner (1948) estimate that 9% of asthmatics are aspirin-sensitive, and death following its use is not rare. The administration of a single tablet of tab. codein. co. or of aspirin, phenacetin, and caffeine can cause status asthmaticus and death.

The severe intractable case of chronic asthma, often beginning in middle age and failing to respond to any form of treatment, remains to be discussed. The prognosis in regard to expectation of life is bad. Desperate measures are justifiable, and in such patients surgery may have a place. Bilateral resection of the pulmonary plexus by interrupting the vagal supply to the lungs is reported to have been successful in some cases (Rienhoff and Gay, 1938).

Conclusion

In conclusion, it is perhaps not out of place to point out that asthma is not only a trying disease for both patient and doctor, but that it not infrequently causes death. The rarity of death from asthma is overstressed in textbooks : whilst it would be unwise for the patient to be undeceived, doctors should realize the true position. Flensborg (1945) states that, of 378 children admitted to hospital with asthma between 1926 and 1939, 15 (5%) out of 298 patients traced had died before 1945. A follow-up of some of my own cases has shown a surprisingly high death rate : in one family two children died in status asthmaticus at the ages of 11 and 18 years. A predominant psychological factor is no bar to a fatal outcome. The immediate cause of death is varied and includes secondary infection with bronchopneumonia, status asthmaticus, and the effect of aspirin in sensitive patients or of morphine. Rarely, death follows the administration of adrenaline, probably delivered accidentally into a vein, or an overdose of a desensitizing solution. The death rate from associated

conditions not apparently related to the asthma may also be higher than for the normal individual. These hazards must be recognized and their risk reduced by careful and thorough treatment at an early stage, and at all times the serious nature of the disease must be appreciated.

(All doses mentioned in this paper apply to adults: appropriate reduction should be made for children.)

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LIFE OF THE RED CELL

The second Frederick Price Lecture was delivered by Professor L. J. WITTS at Trinity College, Dublin, on May 18, his theme being "The Life of the Red Blood Cell." He began by emphasizing the value of co-operation between the basic scientist and the clinician. Over ten years ago the late Professor D'Arcy Thompson had asked him why he thought the red cell was the shape it is. It was interesting to hear a great biologist asking why and not merely how, because Professor Witts was one of those who believed that one of the characteristics of vital processes was their purposive nature.

The red cell was a biconcave disk, he said, first, because that shape was the ideal compromise between a haemoglobin container, which would be a sphere, and a tonometer, which would be a thin disk. Secondly, it was the best shape for low viscosity of the blood and easy flow through the capillaries. It was difficult to explain how the erythrocyte resisted the surface forces which might have been expected to shape it into a spheroidal droplet. There must be an ultramicroscopic architecture of the outer wall and the stroma. Evidence suggested that an important part was played by the nature and orientation of the haemoglobin molecules with which the cell was so closely packed. In certain hereditary diseases in which the red cell was abnormal in shape its viability was reduced, and the patients suffered from a haemolytic anaemia.

New Methods of Measuring

One of the big advances in haematology in the last 20 years was that they could now measure the process of blood formation and destruction in man with reasonable accuracy and simplicity. The reticulocyte count and the output of pigment in the stools could not be used for exact analysis, though they remained useful in clinical work. One of the oldest methods of determining the life of the red cell was to watch the return of the blood to a normal level after haemorrhage or artificial plethora. This method was not theoretically satisfactory, because the normal course of blood formation and destruction was disturbed by those procedures.

All modern methods depended on the formation or introduction of marked red cells in the organism. The marking of red cells depended on the fact that certain characteristics, such as the blood-group substance and the haemoglobin molecule, including the relevant fractions which were analysed, were stable throughout the life of the cell and were not exchanged with other red cells or with the rest of the body. The improved Ashby technique was used in the second world war for determining the best method of storing blood for transfusion. It was found that *in vitro* changes in the fragility, volume, and chemical properties of stored blood cells bore no direct relationship to survival in the recipient, since the cells could recondition themselves *in vivo* after certain types of exposure and not after others. At that time it was discovered that red cells survived up to about 120 days *in vivo* and that with appropriate care and the use of solutions containing dextrose they could be stored up to about three weeks. The survival of red cells in different forms of anaemia was then studied, particularly in those forms where there was other evidence that blood destruction was accelerated.

Dacie and Mollison had found that normal erythrocytes injected into patients with acholuric jaundice survived as long as in recipients without haemolytic disease, the survival periods being from 100 to 130 days. When spherocytic cells were injected into normal people they disappeared completely within 14 to 19 days. Similar results had been obtained in paroxysmal nocturnal haemoglobinuria, pernicious anaemia, and sickle-cell anaemia. In all these conditions the evidence was that the red cell was abnormal from its birth, but that its environment was normal.

Very different results were obtained when similar experiments were carried out in cases of acquired haemolytic anaemia in which haemolysins were present in the plasma or the environment was otherwise at fault. Loutit had found that normal red cells were rapidly destroyed by patients with acquired haemolytic anaemia, whereas cells of acquired haemolytic anaemia transfused into normal recipients survived normally. That finding indicated that red cells which had lived dangerously might be capable of recovery and normal survival when transfused to a healthy environment. That was not always true. Foy and his colleagues had found that transfused cells were extremely rapidly destroyed in the active phases of blackwater fever. The patient's own cells which escaped destruction during the acute crisis were nevertheless irreversibly damaged by the haemolytic mechanism, and their survival was brief, whether in the patient's circulation or transfused to a normal environment. In haemolytic disease of the newborn, Rh-positive erythrocytes were rapidly destroyed, but Rh-negative erythrocytes survived for about the normal 100 days.

Survival Curve

By treating the data of red-cell survival mathematically Professor Witts and his colleagues had found that in normal men the survival curve was rectilinear, reaching the base line at about 120 days from transfusion, and it corresponded with Schiodt's theory of longevity. The straight line indicated that the mixed population of cells of all ages which had been transfused was dying up to expectation. In haemolytic anaemia the survival curve not only reached the axis earlier but was curvilinear—that is, there was an exponential component, corresponding with Schiodt's theory of destruction. In healthy men there was no exponential component, and the average life and theoretical longevity were the same. In women the survival curve seemed normally to be slightly curvilinear because of an exponential component, which was larger than could be explained by the losses at menstruation.

Recent work on the biosynthesis of haemoglobin indicated that the iron of the haemoglobin molecule was derived either from dietary iron or, apparently preferentially, from the destroyed red cell itself. The porphyrin appeared to be freshly synthesized from simple precursors such as glycine and acetic acid, while amino-acids from the dietary protein were used in the synthesis of globin. Each of those three fractions had been used in determining the haemopoietic equilibrium by means of isotopes. Methods based on the synthesis of haemoglobin from isotopes had the advantage that it might be possible to determine the rate of formation of red cells as well as that of destruction.

In America red cells tagged with radioactive iron had been stored under test conditions and then transfused and followed in a recipient. It was possible to measure the mechanical and osmotic fragility of the tagged cells and to show that their mechanical fragility increased in their old age. The re-utilization of radioactive iron for haemoglobin synthesis might be prevented either because the marrow of the recipient was producing little or no blood, as in aplastic anaemia, or when the iron stores of the organism were greatly enlarged, as by treatment with intravenous injections of iron.

Determining the life of red cells by means of radioactive iron gave values of 100 to 120 days. If a small dose of radioactive iron was given intravenously it was possible to determine the rate at which the plasma was cleared of iron, and also to determine the amount of iron going into the red cells. From those data, together with a knowledge of the total red-cell mass and the fact that red cells contained about 1 mg. of iron per ml. of red cells, it was possible to calculate the percentage of red-cell iron renewed in 24 hours. This figure was about 0.9% a day, which was in keeping with estimates of red-cell survival.

Labelled Glycine

The most informative method for studying the life and death of the red cell was the administration of glycine labelled with the stable isotope N^{15}. With this could be studied the synthesis, life span, and pattern of destruction of the red cells in one and the same individual. The method was harmless and could be used in health and disease; but labelled glycine was costly, and elaborate apparatus was necessary for the analysis. The pioneer work had been done by Shemin and Rittenberg, who had shown that glycine was a nitrogenous precursor of the porphyrin of haemoglobin. They had shown that, when glycine labelled with N^{15} was administered in man the haem fraction of the haemoglobin contained a comparatively high concentration of N^{15}. They had followed the isotope concentration of the haem for a long time by analysis of the haemin isolated at intervals. The values rose rapidly to a high level, remained practically constant for many weeks, and then fell quite sharply to a low level.

Those results indicated that the haem was not involved in the dynamic metabolic state and was not utilized again for haemoglobin formation. Analysis of the curve gave an average life span of 127 days. Both in health and in the different blood diseases the results for life span obtained with labelled glycine were of the same order as those obtained with the Ashby technique, and the rates of haemoglobin synthesis corresponded with those obtained with radioactive iron.

ADMISSION TO HOSPITAL

REPORT OF E.B.S.

The report of the Emergency Bed Service for the year ended March 31, 1950, has now been issued. It opens by saying that in the winter of 1948–9 a well-nigh unbearable load was thrown on the service, which was unable to maintain the standards of speed and efficiency that had previously prevailed. In the summer of 1949 a careful investigation was made of the previous winter's work with a view to finding out what were the main causes of difficulty and how to remedy them. It was decided that the best remedy would be to decentralize the work of the service by opening four branch offices in the London suburbs, which would carry part of the load which had previously been borne at Old Jewry.

The result of the reorganization has been to improve both the speed of admission of individual patients and the proportion of patients admitted, in spite of the fact that the total number of applications has increased very considerably. This improvement is due partly to the advantages of decentralization, which has resulted in a closer co-operation between the service and suburban hospitals, partly to an increase in staff, and partly to an increase in the number of hospital beds.

There is a further indication that the bed situation improved in the winter of 1949–50. On 24 days in the previous winter beds were so scarce that by the evening it was impossible to admit adult medical cases unless the case was a life-or-death emergency. Orders therefore had to be given that no such cases were to be accepted by the service for the rest of the day unless the general practitioner stated that the case was one of "life or death." This winter, although the volume of work has greatly increased, no such deadlock has been reached and no case has been rejected by the service without an attempt being made to find a bed.

The agreement by which the service worked for the four Metropolitan regional hospital boards was originally intended to last for an experimental period of two years from July 5, 1948. The experiment has proved useful, and a new agreement has been reached whereby the service carries on for a further two years and thereafter indefinitely, subject to six months' notice by either party. The financial arrangements remain unchanged, the King Edward's Hospital Fund paying the first £6,500, which was the cost of the service in 1947, and the four boards sharing anything in excess of that sum.

Record of Work

The total number of applications received during the year ended March 31, 1950, was: general acute cases, 42,732; infectious cases, 14,506; chronic sick cases, 3,411; total, 60,649. This total compares with 53,798 during the first year of the National Health Service, part of which falls under the period of this report.

Acute Cases.—Of the 42,732 acute cases offered, 34,575 were admitted, and 2,488 withdrawn by the applicant. For the remaining 5,669 no beds could be found, and they were referred back to the applicant. In 1,070 of these cases the applicant was a hospital, and the patient was in the casualty department but could not be admitted to the wards owing to their lack of beds.

During the winter it was found that once again there was difficulty in admitting patients over 60 years of age, although the situation has improved since the first winter of the Health Service. Nearly all age groups show improvement over last year, the greatest being in the age group 51–60, where the percentage admitted increased by 8.1%. The exception is in the age group 0–20, which shows a reduction of 0.4% largely owing to the number of cases of bronchopneumonia in children which it proved impossible to admit during January.

Infectious Cases.—Infectious cases, within the limitations imposed on certain cases by the local public health authorities, have once again caused no serious difficulty, although on occasions it has been necessary to invoke the assistance of the group medical referees for the admission of cases of gastro-enteritis.

Chronic-sick Cases.—The system of dealing with applications for inclusion on chronic-sick waiting-lists was revised in November, 1949. The records of chronic-sick cases were then transferred to the four branch offices, which became responsible for the allocation of cases to the waiting-list of the appropriate hospital management committee, which then takes the responsibility for dealing with the case. This work is done under the direct supervision of the regional medical admissions officers attached to the service, who check that the case is suitable for a waiting-list and obtain a report on the social circumstances when necessary.

The new machinery is working satisfactorily, but the hospital management committees will continue to experience great difficulties in regard to these cases so long as the facilities for dealing with the chronic sick remain so inadequate. Until the situation improves it is difficult to see how waiting-lists can be materially reduced. Since March 1, 1950, the details of every case have been sent to the appropriate hospital management committee on the day of application.

Provincial and Branch Offices

There are branches of the service at Chelmsford, Watford, Brighton, and Tunbridge Wells. These offices are under the operational control of the service, and the cost is a direct charge to the boards concerned.

The branch offices were opened at Leytonstone, Ealing, Woolwich, and Wimbledon. They all work closely in co-operation and are connected to Old Jewry by direct telephone lines. These offices operate from 8.30 a.m. to 9 p.m. daily. The considerable increase in the number of applications received and in the percentage which have been admitted is due in no small measure to the branch offices. They have been able to establish cordial

relations with the local hospitals and doctors to an extent which is not possible with a centralized organization, and they do about 42% of the work of the service.

Medical Referees

A new method has been introduced for the disposal of cases for which the service cannot find a bed. They are referred to the regional medical admissions officers, who formerly were confronted with the choice of referring the case back to the general practitioner as impossible to admit, or of themselves ringing a regional board hospital and requiring it to accept the case. This was a difficult decision to make, and the power of enforcement had to be used as little as possible.

Early in 1949 hospital management committees in the four regions were asked by the regional boards to appoint a senior hospital officer in their group to whom the R.M.A.O. could refer an urgent case, and who would be responsible for finding a bed in the group or for making certain that there was no bed available. Since appointment of the group medical referees in January, 1949, 1,005 cases have been referred to them, the largest monthly total being for January, 1950, when there were 189, which is 2.5% of the total applications that month. In many cases the medical referee discusses the case with the general practitioner and is able either to arrange to admit within the next day or two or to suggest a visit by a consultant.

Time Taken to Admit Cases

In addition to being able to admit a higher proportion of cases than last winter, the opening of the branch offices has enabled cases to be dealt with more expeditiously and efficiently. In the winter of 1948–9 the average time taken to admit a case was 56 minutes; this winter it has been reduced to 42 minutes. In order to obtain admission for any patient it was found necessary to approach an average of 3.36 hospitals in each case compared with 3.64 in the previous winter.

Where the patient was not admitted the average time taken to conclude the case in the winter of 1948–9 was 3 hours 54 minutes, in the course of which an average of 5.15 hospitals were tried. This year the average time was 2 hours 25 minutes, an average of 7.05 hospitals being approached before failure was admitted. These averages are for all cases dealt with in Greater London during a sample week in February. The figures for Old Jewry as distinct from branch offices were 45 minutes to admit a case and 2 hours 42 minutes on cases for which no bed could be found.

THE CARE OF CRIPPLES

In presenting the report at the annual general meeting of the Central Council for the Care of Cripples on May 19 Mr. J. Rhaiadr Jones said that the council was the co-ordinating body for all organizations working for the care of the crippled. Ministries and local authorities were showing greater interest than ever in the work of the council, and orthopaedic hospitals, although now under the National Health Service, continued to be affiliated members. Development work—the promotion of county and regional associations concerned with all aspects of the care and welfare of the crippled in the area—had continued actively, and the number of inquiries from and about individual cripples showed no signs of decreasing. The first training-course for welfare officers arranged by the council had been completed, and there would probably be further courses on the same lines, although it was not intended that they should all be held in London. Examinations for orthopaedic nurses had been held by the Joint Examination Board of the British Orthopaedic Association and the Central Council, and the question of nursing examinations in the future had been considered.

It was announced that during the past year Lord Nuffield had become president of the Central Council. The previous presidents have been the late Sir Robert Jones and the late Dame Agnes Hunt. A school for crippled children had been established by the Central Council at Hesley Hall, and would be opened by the Queen in July. Some £7,000 had still to be raised in connexion with this school.

After the meeting an address was given by Dr. Henry Kessler, president of the International Society for the Welfare of Cripples. Dr. Kessler paid tribute, on behalf of the International Society, to the work done by the Central Council. He defined the object of all help for cripples as being to make help superfluous. One of the most serious obstacles was public prejudice. Many still regarded disablement as being due to evil, though they might try to rationalize this primitive instinct by saying that they would employ a cripple if it could be proved that the cripple would do a full day's work, or they would affirm that the cripple was more accident-prone than the average, despite evidence to the contrary. Dr. Kessler described the work being done for cripples in various countries, including Japan. It was intended to hold the fifth International Conference on the Welfare of Cripples in Scandinavia in 1951; the last was held in London in 1939.

The Earl of Dudley, who presided at the meeting, was re-elected chairman of the Central Council.

Reports of Societies

HABITUAL ABORTION

LECTURE TO ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The biennial Scholarship (Sterility) Lecture was delivered to the Royal College of Obstetricians and Gynaecologists on May 19 by Mr. LINTON MORRIS SNAITH. This is an Anglo-American lecture given every two years alternately by American and British gynaecologists.

Mr. Snaith, who took as his subject "Habitual Abortion," said that this problem had received inadequate attention in gynaecology. Abortion cases were almost completely excluded from the wards of teaching hospitals, and the habitual abortion syndrome received scant notice in textbooks. Theories on the causes of abortion were as numerous as the proposed treatments. The expectation of normal pregnancy after abortion was stated by Malpas, after a survey of 6,000 pregnancies, to be 78% following one abortion, 67% following two, 27% following three, and 6% following four. Eastman (United States) found similar figures, except that after three abortions there were normal pregnancies in only 16.4%.

Aetiology

The early theories involved the conception of defective maternal environment; more recently, germ plasm defects, male and female, had been considered, and the Rh factor had been studied. The survey on which he was reporting lent no support to older theories and very little to existing ones. Syphilis in the mother was found in only two of the cases; in two others the father was under treatment, but the mother was uninfected. Hypertension, pre-existent or disclosed early in pregnancy, was found in only six cases in his series. The Rh factor was investigated in many cases, but there was no abnormal incidence of the Rh-negative state, and he thought there was no evidence that this state was a significant factor in his own or other series. He had investigated male infertility in relatively few cases. His findings and a study of the reports of others had led him to abandon the investigation as a routine except where the patient requested it, or where there was unusual delay in conception. A colleague had reported that one type of sperm defect appeared more frequently than others in abortion cases, and this was being followed up. In 33 of the cases examined the man was unquestionably perfectly fertile, in eight sub-fertile, and in eight doubtful. His conclusion was that the sperm was not normally responsible, at least for habitual abortions.

Those who put forward retroversion as a cause of abortion seemed to forget the very high incidence of retroversion in

women who went to full term. He had an impression that there was a higher incidence of retroversion in cases displaying initial abortion—that is, abortion in the first pregnancy.

Progesterone and Vitamin E

Turning to the effect of progesterone and vitamin E, Mr. Snaith said that the belief in the value of progesterone was based on a series of experimental observations and clinical reports, most of them on small numbers of cases. The experimental work was conflicting. Some of it indicated that progesterone had a sedative effect on the uterine muscle. Clinical reports were numerous, but many of them ignored or did not make due allowance for the probability of chance cures. The Council of Pharmacy of the American Medical Association, reviewing the claims for progesterone, found the case far from proved. Vitamin E was almost traditional in this connexion; the difficulty was to find a case in which it had not been administered after only one abortion. The Council of Pharmacy found that there was no convincing experimental or clinical evidence but that further trials were justified. One point of importance was that those who favoured vitamin E emphasized that very large doses were required, far in excess of the amounts usually given.

On the incidence of defect in the embryo, all authorities agreed that examination of the products of conception in abortion revealed a high percentage of defects in the foetus. Absence of embryo or presence of distorted embryo had been reported. After showing certain tables Mr. Snaith said that the very high incidence of defective embryos struck him as significant. The name now commonly applied to this type of abortion was "blighted ovum." He had now had the opportunity of following up about 100 cases in which the end-result had been blighted ovum. The majority were initial pregnancies. He had formulated a typical case-history of the condition. Before pregnancy the patient often presented some of the signs of genital hypoplasia. In the first six weeks she showed few of the so-called signs of pregnancy, and when first seen there was doubt whether pregnancy existed.

The cause of blighted ovum was a matter of speculation. It had been shown in the lower animals that defective ova could exist and might be fertilized. There seemed to be some evidence that failure of pregnancy in the human was associated with, if not due to, defect in the ovum; this defect might be primary, but might also be produced by a defective environment which could be rectified by treatment in the earlier stages of pregnancy. It seemed to be possible that many of the random factors were merely trigger mechanisms setting off the real causes of abortion. Perhaps the majority of treatments were wasted, because the abortion was in any case inevitable and many successful amateur abortionists had only been anticipating nature.

Value of Oestrogens

The comparative failure of other methods of treatment had led many people to try the effect of oestrogen given from a very early date in pregnancy. A satisfying series of cases treated by oestrogen only, preferably subdivided into early and late abortion sequences, was awaited. Less than half the cases in his department had been treated by oestrogen alone. Such results as were available from oestrogen therapy alone were good. He began by giving 5–10 mg. of oestrogen daily in such cases, but later adopted a dosage of 15 mg. daily as soon as the patient was a week overdue in the regular cycle, and a fortnight later this was increased to 20 mg., and later increased again. One could only speculate on the reason for the effect of oestrogen—it might diminish irritability, cause relaxation of the uterus, produce a vasodilatation, possibly assist the growth of the uterus, encourage utilization of carbohydrate, or prevent decidual bleeding.

His results with oestrogen therapy, which he put forward in a table, were, he said, optimistic; but to offset undue optimism he showed also tables giving somewhat similar results in a group of cases which had had other treatment or no treatment at all beyond ordinary antenatal care.

Summing up his lecture, Mr. Snaith said that the points he had tried to demonstrate were:

(1) That there is a high reported incidence of defective embryos in abortion; that many cases of threatened abortion were really inevitable, and any treatment must be started very early to be of value.

(2) That there is no real evidence for the part played by progesterone or vitamin E in the prevention or treatment of abortion.

(3) That administration of oestrogen in large doses is well tolerated, and the results are satisfactory. There is no evidence of resulting harm.

(4) There is no evidence for the action of an Rh factor in abortion.

(5) Further investigation is desirable into the effect of oestrogen in early pregnancy, possibly by biopsy, assessment of glycogen content, etc. He hoped that all reported series of abortions would include an analysis of the number of defective embryos and a division into early and late pregnancies.

Preparations and Appliances

A TECHNIQUE FOR A FINE SCAR IN THORACIC SURGERY

Dr. J. HAMILTON GIFFORD, medical registrar, Fazakerley Sanatorium, Liverpool, writes: The importance of obtaining an unobtrusive scar following surgical incisions has long been recognized, and numerous methods and devices have been evolved with this object in view. The lengthy periscapular incisions employed in thoracic surgery demand special attention, particularly in female patients. For two years a routine based on that evolved by Overholt has been followed at Fazakerley Sanatorium, and has given very gratifying results.

Alternate skin sutures are removed on the third post-operative day and the remainder on the sixth day. The marks left by the sutures are almost invisible, but the incision must be adequately supported until the tenth or twelfth day, according to the rate of healing, or widening of the scar will result. If the sutures are left *in situ* for the longer period they tend to cut in and leave scars themselves, the cutting-in then allowing the incisional scar to widen.

In periscapular incisions, scapular movement throws considerable strain on the scar, and as repeated exercises are carried out by the patient in order to restore full arm and shoulder movements efficient support must be provided if widening of the scar is to be prevented. Overholt uses adhesive strapping, and at the Fazakerley branch of the Liverpool Regional Thoracic Unit we have evolved our own technique, which has proved highly successful. The few instances of partial wound dehiscence which have occurred all followed either superficial or deep wound infection, and dehiscence would have been expected no matter what treatment the wound had received.

The dressing should be inelastic and not adhere to the scar; also the scar should be readily available to inspection and have adequate ventilation. We therefore employed H-shaped pieces

of zinc-oxide adhesive strapping, cut from a 3-in. (7.5-cm.) roll. The pieces cut in order to form the bar of the H were not removed, but were folded in on to the adhesive surface of the bar, thus rendering it non-adhesive.

The dressings are employed in the following manner. The skin on each side of the incision is painted with tinct. benzoin. co. and allowed to dry. This is important, because if moist the adhesive quality of the plaster is destroyed, but when dry it is enhanced. One upright of the H is applied parallel to and ½ in. (1.27 cm.) to one side of the incision. The skin is then drawn up towards it and the opposite upright is firmly stuck down on the opposite side. Further pieces of strapping are then applied below in succession along the course of the incision, slightly overlapping each other at an angle on the outer side of the curve, and more so on the inner side according to the degree of curvature. The final appearance is as shown in the accompanying photograph.

Dressings of zinc-oxide plaster already cut to the pattern described, and adhesive only along the upright portions, can now be obtained from Messrs. Edward Taylor, Ltd., Monton, Lancashire, who are perfecting a transparent plastic dressing made to my requirements. This will render the full length of the scar visible at a glance.

I am indebted to Mr. F. Ronald Edwards, thoracic surgeon to the Liverpool Regional Thoracic Unit, for suggesting the routine; to Sister H. Doran for her invaluable assistance in making the original dressings; and to Messrs. Edward Taylor, Ltd., and their representatives for their interest and co-operation.

Correspondence

Double Primary Carcinoma

SIR,—I have been much interested in the medical memorandum on synchronous double primary carcinomata by Dr. T. B. Williamson (March 18, p. 648) and Dr. M. L. Farmer's letter (April 15, p. 905) on the same subject. As Dr. Williamson points out, multiple carcinomata may occur in as many as 5% of carcinoma cases, but subsequent growths are commoner than synchronous ones. The latter are rather likely to be missed.

I am sure the lesson to learn and remember about synchronous carcinomata is not so much their rarity but the importance of always looking for a second or even a third carcinoma when one has been found. At present I have two ladies in the same ward under my care both with synchronous double primary carcinomata, one with a growth in each breast and the other with a carcinoma in the rectum as well as in one breast. I have had a patient bearing three primary carcinomata at the same time, one in each breast and another in the colon.

It is very easy to become negligent in the examination of a patient when a carcinoma has been found and carefully examined. One looks for metastases in the ordinary sites, but may well fail to search for another primary. I certainly have overlooked a second primary growth when it has occurred synchronously.

I am amused by Dr. Farmer's recollections of assisting Blair Bell at a radical mastectomy. For cutting a ligature with the point of the scissors instead of the heel he recalls that he "caught a rocket" from Blair Bell. I believe he would be more likely to catch the axillary vein if he cut with the heel instead of the points. I always insist that my assistants cut with the points: I believe it is the only safe way.—I am, etc.,

London, W.1. JOHN HOSFORD.

SIR,—The report by Dr. T. B. Williamson (March 18, p. 648) prompts us to place on record the following case which we have recently encountered.

A housewife, aged 48 years, was admitted to hospital on March 3, 1949, suffering from subacute intestinal obstruction which was found to be due to carcinoma of the colon. An emergency transverse colostomy was carried out, and three weeks later the carcinoma of the lower part of the descending colon was excised by one of us (G. S. A.). There were some enlarged glands in the mesocolon which were also removed. Four weeks later the colostomy was closed and the patient discharged in good condition on May 13, 1949.

She remained in good health until February, 1950, when she reported to hospital with a large swelling of the lower abdomen, apparently arising from the pelvis. Laparotomy on March 2 (J. A. C.) showed a large solid tumour 12 by 8 by 8 in. (30 by 20 by 20 cm.) arising from the left ovary, with multiple secondary nodules in the parietal peritoneum and in the omentum. The uterus and right appendage were normal, and there was no evidence of any activity of the colic carcinoma. The left ovarian tumour was removed, and a week later the patient was transferred to the Royal Northern Infirmary for deep *x*-ray therapy. This was satisfactorily completed, and her condition has since been satisfactory.

Histological examination of the first tumour showed it to be a typical adenocarcinoma of the large bowel, and metastases were present in four of the eight lymph glands removed along with the tumour. The ovarian tumour was a papillary carcinoma with pseudo-acinus formation and histologically quite distinct from the first tumour.

The rapid growth of the ovarian tumour to the size recorded above is noteworthy, since at the primary operation, exactly one year before its removal, it was noted that "the pelvis was clear."

This case conforms to the criteria of Billroth[1] as well as to the less stringent requirements of Warren and Gates[2] for recognition as a case of double primary carcinoma. Slaughter[3] included nine cases involving the colon and the ovary in his remarkable series of 1,868 cases of multiple primary tumours, of which 54.4% were of the same or of paired organs. Berson and Berger[4] have suggested that predisposition is more important in these cases than chance, sex, or age, and this case may lend support to this view and to the statement of Brindley[5] that a patient who has one cancer is a good subject for the development of a second and is more susceptible than one who is cancer free. Indeed, when one considers the possible endocrine, biochemical, or genetic background of cancer, it is remarkable that the figures for the frequency of the multiple primary lesions are as low as the 2–5% suggested by Dr. Williamson and the 0.3–6.8% quoted by Barrett, Miller, and Fessemeyer.[6] Gordon[7] states that cancer arises from the interaction of an extrinsic environmental factor with an intrinsic predisposition and that an increase in the latter may lead to multiple neoplasms.—We are, etc.,

G. S. ANDERSON.
Inverness. J. A. CHALMERS.

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3 *Surg. Gynec. Obstet.*, 1944, **79**, 89.
4 Ibid., 1945, **80**, 75.
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Maternity and the N.H.S.

SIR,—The recent correspondence on Maternity in the N.H.S. together with the report (May 13, p. 1130) of the discussion on the same subject at the Royal Sanitary Institute Congress show, if I may say so without offence, widespread confusion of thought or ignorance of practice. We all want the best maternity service, but will it be obtained, as Professor James Young seems to think, by unifying control at the top? I think that anyone who has had any experience of such control knows by bitter experience that it is physically impossible for the nominal head to exercise the detailed control which is theoretically desirable. The result is that more and more decisions are made by officials and clerks lower down the scale. In medicine this means—as most of us are aware—that medical matters are more and more decided by those who have not had any medical training. Mostly, I know, they do their best and manage very well, but it is an entirely different set-up from that envisaged under the "unified control" for which such high claims are made, and it is by no means the best that can be done.

It would seem much more sensible, and it certainly works much better, to give control of midwifery cases to a properly trained doctor and give him the right to call on all ancillary

services as he thinks fit. The family doctor often knows facts of material importance about a case that the midwife cannot be expected to know and that the gynaecological consultant is unlikely to discover, particularly if the G.P. has lived ten years or more in his practice ; and no doctor with ten years' experience will be content simply to be the stooge of an obstetrician or his clerk if he is fit to be a doctor at all. The Manchester regional hospital board recently did the maternity service in Cheshire the honour of stating that sufficient use was not made of specialists—a very serious statement to make and one well in line with recognized nationalization technique, which is first to denigrate a service and then replace it with one much more expensive, top-heavy, and inefficient.

The Ministry of Health must bear direct responsibility for the lack of maternity homes in this county, but readers of the *B.M.J.* for the past twenty years need little reminding that Cheshire has, in fact, led the way in antenatal services (mainly through the efforts of the late Dr. L. J. Picton) and in making the help and advice of consultants as freely available as possible.

The basis of the Cheshire county scheme (which took over in detail that initiated by Dr. Picton in Winsford over 20 years ago and expanded it as rapidly as Treasury permission could be obtained) was based entirely on giving the general practitioner full control of every service the local authority or hospital services could provide. Any midwife could call in a woman's doctor for any cause she thought desirable, and in such cases the doctor's full fees were paid by the county. If a doctor wished his patient to go to a clinic or hospital this was provided gratis. If, on the other hand, the doctor wished a consultant to visit his patient at home before, during, or after labour the county paid for that too, and the list of consultants who were willing to undertake these visits was constantly expanding. As a result of this scheme there was the freest possible co-operation between doctors and consultants, but the inevitable and right result was that doctors, with this postgraduate service at their elbow, in time learned how to treat their patients better and so required less and less expert assistance. This, however, was not a fault in the scheme ; it meant that the scheme was being a success and raising the whole standard of midwifery in the best possible way. If the obstetrician is given the right to nose into every case the only result can be to detract from the responsibility and interest of the doctor, whereas when the doctor calls in the consultant his interest is stimulated without diminishing his final responsibility for his patient.

But regional boards and the Ministry seem to treat G.P.s as if they were ignorant, with no sense of responsibility, in fact with little sense at all. They will have only themselves to blame if doctors do, in fact, accept the role allotted to them, routinely and somewhat sullenly going about their work, resentful of the position into which they have been forced and dimly aware that the great heritage and freedom of medicine is being stifled by red tape and uncomprehending bureaucracy. It is tragic that two years of the National Health Service should have debased general practice as it has and that many so-called leaders of the profession seem anxious to depress it further still. If the patient gained it would not matter, but he, and particularly she, doesn't ; nor can improvement be expected until doctors are treated as reasonably intelligent human beings.—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

SIR,—It was hardly surprising that Professor James Young (April 22, p. 955) did not attempt to reply to all the criticisms of his lecture to the College of Midwives (February 18, p. 392). It is true that there was a modicum of approval, chiefly from the administrative angle, but for the most part its reception seemed to be decidedly chilly.

The trouble with the "planners" is, of course, that they are quite out of touch with the realities of the situation. We hear a lot about the "control" of the pregnant woman, and of the "regulation" (how sick we are of the word) of the general practitioner's part in the maternity service. It is quite time that some attention was paid to the wishes of the patients. When they come along, as they still continue to do much as before, to their doctors and ask to be attended, is anybody—the Minister, the planners, or the R.C.O.G.—going to forbid it ? If so, what becomes of free choice ?

Here, however, I would venture with all due respect a word of warning to my fellow practitioners. If they fall into the snare so insidiously inserted in the regulations and provide for the patient the minimum services, their obstetric practice will vanish like the snow in May. The patients will find them out and will certainly not be so obtuse as to fail to recognize it for the sham and pretence that it is. All the same, it is a grievous matter that such a temptation to "easy money" should have been thrown out to the younger men.

Professor Young writes in his letter that "continuity of supervision is possible only when midwife, doctor, and clinic and hospital officers are linked as a team." In actual fact, of course, it is exactly this division and subdivision of responsibility which make continuity impossible. On the other hand, as Dr. Joan Wagstaff (March 4, p. 550) pointed out, the general practitioner really is in a unique position to supervise the whole thing—the antenatal period, the labour, the puerperium, and any necessary post-natal investigations. He is, in fact, the *only* one who can exercise such complete and continuous responsibility, and nowadays he has in many places the advantages of facilities for blood grouping and rhesus tests, *x* rays, availability of flying squads and obstetric consultants in emergencies, and, generally, the willing admission of a necessary case to hospital. One should in fairness point out these things, as they are to some extent an actual improvement under the new Act.

I would venture to urge all those who believe in the future of obstetrics in general practice not to lend themselves to a scheme which is really a travesty of the art, which offers a wholly illusory kind of "cover" to the midwives, and in doing so is not even fair to them. It is in fact a hybrid system which pleases nobody, because it pretends to be what it is not. Provided always they know what they are going to get, the patients themselves can decide quite easily how and by whom they wish these services to be rendered.

I submit that if the service is based upon free choice by the patients, and if the general practitioner is sufficiently interested in midwifery to give full and complete care all the way through, he can, remembering always the meaning of the word "obstetrics," provide the best service for his patients, though admittedly the remuneration for such a service is inadequate. In this way not only will the general practitioner attain a steady experience in midwifery, but will acquire and maintain a degree of efficiency (unobtainable in any other way) which is indispensable and of vital interest to the patients and the midwife when the emergency calls come.—I am, etc.,

London, N.W.7. A. H. MORLEY.

A New Method of Bronchography

SIR,—Drs. D. E. Vaughan Jones and M. R. William Spacek (May 13, p. 1140) describe a technique for the introduction of radio-opaque oil into the trachea for bronchography. They advise the passage into the trachea of a Magill tube in the lumen of which is another tube of 4 mm. outer diameter, through which the oil is to be injected. This method gives adequate results in adults but in our hands has not proved satisfactory in children, because in the latter the lumen of the small endotracheal tube is practically obliterated by the inner tube for oil, so that respiration is seriously impaired. We dispense with an endotracheal breathing tube both in adults and in children. After the reflexes of larynx and trachea have been obliterated (we use cocaine in appropriate dosage) a fine rubber tube is passed directly into the trachea either "blindly" or under direct vision. Even in the smallest children on whom bronchography is likely to be performed this fine rubber tube (e.g., Magill 00), through which the oil is subsequently injected, takes up only a small part of the laryngeal opening and respiration continues freely around it.—We are, etc.,

R. R. MACINTOSH,
Nuffield Professor of Anaesthetics, Oxford University.

WILLIAM W. MUSHIN,
Director, Department of Anaesthetics, Welsh National School of Medicine.

SIR,—With reference to the technique of bronchography suggested by Drs. D. E. Vaughan Jones and M. R. William Spacek (May 13, p. 1140), I feel that to intubate the trachea blindly is an unjustifiable procedure when a simpler alternative method is available. I refer to the Singer method, which is used as a routine at the thoracic surgical centre in the Baguley Emergency Hospital, Wythenshawe. The method can be used on intelligent children of 12 years, and out of fifty patients in which it has been used this year only three have been found to be definitely unsuitable.—I am, etc.,

Manchester. D. C. LINDARS.

Ankle Amputation

SIR,—I am glad to see Mr. W. Gissane (April 15, p. 901) and Mr. Leon Gillis (May 13, p. 1139) advocating the claims of Syme's operation for ankle amputation, as I have often thought it was a pity such an excellent method had fallen into disrepute. I attended John Chiene's lectures on surgery in 1894. John Chiene had been Syme's assistant. He told us that Syme always made his primary incision right down to the bone. He said that was a most important point in order to get a successful result.—I am, etc.,

Newton Abbot, Devon. W. H. STEELE.

Anaesthesia for Fenestration Operation

SIR,—There has been much interesting correspondence in the *Journal* about the fenestration operation, and I shall be grateful if I can add something further on this subject.

I have administered several hundred anaesthetics for this operation performed via the transtympanic route. Most anaesthetic agents and various methods were tried in order to determine the safest anaesthetic which would also produce the minimum capillary oozing. We found cyclopropane to be most unsuitable, producing the maximum of bleeding, while with thiopentone administered continuously, although bleeding was not so marked, it was felt that unless an intratracheal tube was inserted one had little control in preventing a laryngeal spasm. Several years ago I thought trichlorethylene to be the ideal anaesthetic for this type of operation, but when two patients showed the alarming signs of chloroform poisoning, and with the knowledge that several fatalities had been recorded, I immediately called a halt.

I am now of strong opinion, and so is Mr. Otto Popper, for whom I have been administering these anaesthetics, that ether with gas and oxygen, or preferably with oxygen alone, delivered through a large intratracheal tube by the semi-closed method is the anaesthetic of choice. The mouth is not packed off, and the expiratory valve is left completely open. The head is placed on its side, but in the "air-sniffing" position, as described by Professor R. R. Macintosh. Thus a perfect airway is created, resulting in no congestion, which is one of the main causes of oozing. The anaesthetist is always in a position of complete control and the depth of anaesthesia can be easily regulated. The minimum amount of ether is required to maintain the type of light anaesthesia required for this operation. It is always possible for the facial reflexes to be present at the termination, in order that a check be made to determine any pressure on the facial nerve.—I am, etc.,

Johannesburg. H. H. SAMSON.

Mongolism in One of Twins

SIR,—I would like to make some remarks on the medical memorandum on mongolism in one of twins by Dr. A. R. Graham (March 25, p. 706). In my paper on the importance of twin pathology in paediatrics[1] I reported on 46 pairs of twins, 22 of different and 24 of the same sex, where only one of the twins developed mongolism. There were seven pairs of uniovular twins, one pair under my own observation, where both twins developed mongolian idiocy. Warner[2] reported on 30 pairs of twins of different sex in which one of the twins had been affected; while in 16 pairs, in which likewise one of the twins had been affected, the sex had not been stated. Out of 37 pairs of like-sexed twins, only one of the twins had been affected. Therefore there are 82 pairs of twins reported in the literature in which one of the twins developed mongolism. As there are 18 more pairs in which the sex has been stated and in which both of the twins developed mongolism, and two more pairs without any statement of the sex but with mongolism in both of the twins, there are in all 102 pairs of twins reported so far in the literature, in which one (82 instances) or both (20 instances) of the twins developed mongolian idiocy. As to the British literature, Dr. Graham claims that Armstrong's case in 1928 was the last to be reported. So far as I can find from the literature, there was a case reported by Russel in 1933.[3]—I am, etc.,

University of the Philippines, Manila. EUGENE STRANSKY.

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Intestinal Obstruction Due to Food

SIR,—Mr. Neil Ward-McQuaid's interesting and comprehensive article (May 13, p. 1106) on intestinal obstruction due to food prompts me to report this similar case met with at Whipps Cross Hospital.

A lady aged 68 was admitted to hospital on July 20, 1948. She had suffered from severe continuous abdominal pain for the three previous days. The pain was generalized at first and had later shifted into the right iliac fossa. She had vomited several times. Her bowels had been open since the onset of pain. Micturition was normal. Her temperature was 98.8° F. (37.1° C.), and pulse rate 100. Her tongue was dirty. The abdomen was not distended, but was extremely tender in the right iliac fossa. On rectal examination there was tenderness on the right side.

With a provisional diagnosis of acute appendicitis the abdomen was opened through a right paramedian incision. Collapsed coils of small intestine, when traced upwards, led to what appeared to be a gall-stone obstruction about four feet from the ileo-caecal valve. The bowel was opened and the "stone" removed. It was 2½ in. (6.25 cm.) long, 1½ in. (3 cm.) wide, 1 in. (2.5 cm.) thick, and weighed 5.75 g. The intestine was closed transversely, and she made a good recovery, except that she had a small pulmonary embolism on the thirteenth day after operation. This cleared up with heparin and dicoumarol, and she was discharged from hospital on August 21, 1948.

The stone on section was found to consist of tomato skins tightly rolled into long cylinders and closely packed together. They were held together by hard faecal material.

The patient recollected eating tomatoes in a salad a few days before the onset of symptoms, but could not remember the number. I note that Mr. Ward-McQuaid has not recorded obstruction due to tomatoes in his list.—I am, etc.,

London, E.11. S. G. NARDELL.

SIR,—I read with great interest the article by Mr. N. Ward-McQuaid on intestinal obstruction due to food (May 13, p. 1106). Between the years 1943–6 I had the opportunity of dealing with three cases of this nature. I would like to record these, and so add to the total of 178 cases traced by Mr. Ward-McQuaid.

Case 1.—A female patient aged 56 was admitted to hospital in February, 1944. The patient looked very ill, being markedly dehydrated and cachectic. Her temperature was 98.4° F. (36.9° C.), pulse 88. The history obtained was that she had suffered from severe generalized abdominal pain for the past two days. She had also vomited several times. Similar attacks of abdominal colic had occurred during the previous two months. Examination of the abdomen revealed tenderness in all areas. Rectal examination was negative. A diagnosis of intestinal obstruction was made, and the patient was put on an intravenous glucose-saline drip preparatory to operation. Consent for this was not obtained immediately.

The following day the patient's general condition had improved. Borborygmi could be heard in the abdomen, and brownish fluid was being aspirated from an indwelling Ryle's tube. A tender ill-defined mass could be felt in the right iliac fossa. Consent for operation was ultimately obtained, and the abdomen was opened under spinal analgesia by a right lower paramedian incision. Free fluid was present in

fair quantity, and also loops of collapsed and distended small bowel. The obstructing agent was felt to be a soft cylindrical mass inside the lumen of the small intestine. Enterotomy was performed, and the mass was found to be half a peach. The bowel and abdomen were closed. It was learned later from the patient that she had swallowed half a dried peach two months previously. Convalescence was uneventful until four weeks after operation, when she developed an acute psychosis and had to be removed to a mental institution.

Case 2.—A female patient aged 54 was admitted to hospital on April 26, 1945, complaining of abdominal pain and vomiting. The pain, of four days' duration, was central in origin. Her temperature was 99° F. (37.2° C.) and pulse 108. The abdomen was somewhat distended and tender on pressure. Peristaltic sounds were active. She had an old sub-umbilical median scar from a previous hysterectomy. A diagnosis of intestinal obstruction due to adhesions was made, and she was placed on an intravenous drip, together with an indwelling Ryle's tube. Operation was performed under spinal analgesia through a right lower paramedian incision. Free fluid was present, together with distended and collapsed loops of small bowel. A few adhesions were present, but none were causing the intestinal obstruction. The obstructing agent was some solid intestinal contents about 2½ in. (6.25 cm.) long and filling the lumen of the bowel. The site was about four to five feet from the ileo-caecal junction. The mass could not be broken up, but was milked along the collapsed bowel and threaded through the ileo-caecal junction into the caecum and ascending colon. The abdomen was closed. Apart from slight distension of the abdomen she made an uninterrupted recovery. Careful questioning revealed that she had been eating some dried peaches recently and had swallowed one whole on April 22.

Case 3.—A female patient aged 35 was admitted to hospital in August, 1945. She had been quite well until between 6 and 7 p.m. that evening, when she then developed colicky pain centred around the umbilicus, followed one hour later by vomiting. Her pulse was 68 and temperature 98° F. (36.7° C.). Examination of the abdomen showed nothing abnormal except slight tenderness over the right iliac fossa. Rectal examination was negative. A diagnosis of intestinal obstruction was made and a laparotomy performed under spinal analgesia. Free fluid was present in the peritoneal cavity with distended and collapsed loops of small bowel. A pultaceous mass was found within the lumen of the ileum, 4 ft. from the ileo-caecal junction, and was causing the obstruction. This mass was squeezed along the ileum into the caecum. The patient was then questioned and revealed that she had eaten eight large plums plus their skins at 2 p.m. that same day. The post-operative convalescence was uneventful.

It will be noted that in two of these cases the impacting bolus was a dried peach, the second most common of the obstructing foodstuffs in the list quoted in Mr. Ward-McQuaid's article. Furthermore the peaches were swallowed whole, so that their bulk, intensified by absorption of water in the gastro-intestinal tract, precipitated the obstruction. Case 3 is of particular interest, for it would appear from Mr. Ward-McQuaid's article that this is the only case as yet reported where the obstructing agent was due to plums. The eating of eight large plums at one sitting with hurried and inadequate mastication would in itself be a potent predisposing cause. Case 1 has additional interest in that two months elapsed from the time of ingestion of the dried peach before the patient came to operation. She had had several attacks of "bolus colic" in the interim. In this case also the impacted bolus was palpable on clinical examination as a mass in the right iliac fossa.

As to treatment, my own feeling is that laparotomy is usually called for, as the cause of the obstruction is never quite clear. Once the impacted bolus has been located (its site is usually 3 to 4 ft. from the ileo-caecal junction) I consider that an attempt at milking the mass along the terminal ileum into the caecum and ascending colon is worth trying first. This procedure is less hazardous than enterotomy and in Cases 2 and 3 did not result in paralytic ileus.—I am, etc.,

Southport, Lancs. M. A. GOODWIN.

The G.P. at the Crossroads

SIR,—We must all feel the profoundest sympathy with Dr. E. Anthony (May 6, p. 1077) in the difficulties with which the G.P. is confronted under the N.H.S., and we ought to be grateful to him for the force and clarity of his letter. Clearly the vices of the service which he reveals are not the teething troubles of an otherwise vigorous infant which will in time vanish as the infant gets stronger. They are vices of the heart and brain of an animal which is proving intolerable to decent-minded men and women.

Dr. Anthony is anxious to restore the days when the doctor was approached as a friend to diagnose the patient's ailment and to advise him as to treatment, and in particular to protect him against the snags of his position if specialist or hospital investigation and treatment are necessary. The G.P. will cease to be a pedlar in the scramble for the hand-outs of the "free" State service, in which an appreciable number of the seriously ill will come off worst, and win once more the respect of his patients only if there is restored the right of the individual to contract out of the State scheme and use his money at his own risk to obtain the services of a medical man whom he can respect and trust. This right to contract out is clearly exercised by those who go off to other countries to obtain private medical treatment of which they approve and in which they trust.

The physician and surgeon and accoucheur have enjoyed a very varied status in Western civilization. There have been periods when only chattel slaves exercised these functions. The restoration of the high status of the medical man which we have lost will be achieved only by free men taking proper time to examine and treat a patient as a friend to be restored to health. There is no earthly reason why people contracting out of the N.H.S. should not organize themselves with regard to finance and choice of doctors if they wish, instead of consulting free-lance medical men. A nation which organized the co-operative movement without invoking the State or taking their social and economic theory from Prussia or Karl Marx would find a natural expression of its genius in similar local and varied organization in medicine.—I am, etc.,

Buntingford, Herts. E. H. STRANGE.

SIR,—The Royal Sanitary Institute Congress, reported in the *Journal* of May 13 (p. 1130), adds to the anti-G.P. clamour which seems now to arise on all sides. Not so very long ago there was much talk of the general practitioner as a tireless and devoted man whose clinical acumen was indeed to be the mainstay of the National Health Service, a diagnostician to bring all cases needing such care safely to the hands of the appropriate specialist, a therapist whose armamentarium would no longer be limited by mere considerations of finance—in fact, a thoroughly worthy fellow, to be enticed into the N.H.S. at all costs.

How different is the tale now. There are more G.P.s in the scheme than was bargained for, but the remuneration must not be increased to cover this. The cost of drugs and appliances prescribed by these miserable fellows is too high, and they must see that it is cut down. The G.P. is overloaded with work and is not able properly to examine or treat his patients (according to Dr. H. C. Maurice Williams). His bedside manner is no more than a "veneer of incompetency, with a hope . . . that nature will effect a cure." In some quarters, according to Dr. J. G. Thwaites, it is deemed desirable that the general practitioner should be entirely excluded from the practice of midwifery.

Dr. Barbara J. Hick, in a letter in the same issue (*Supplement*, p. 220), adds to the picture by pointing out that she only receives 5s. for the immunization of a child, while a veterinary surgeon gets no less than a guinea for a like service for a puppy. (Dr. Hick is wrong. She gets no fee for the immunization, but 5s. for filling in the record card.)

Fashion changes in medicine, and one can only hope that the present fashion of decrying the G.P. will be but a fleeting one. There is not the slightest doubt that some of the stone-throwers live in the most vulnerable of glass houses, and one not infrequently has to use the greatest tact and restraint in dealing with other-worldly gentlemen who are full of contempt for the G.P. and equally full of ignorance about his problems. There are good, bad, and indifferent in all walks of life, and this must be accepted in all branches of medicine. On the whole the normal laws of economic survival apply, and the public is loath to endure bad service. A "popular" doctor is usually painstaking and careful, and the day of the man who is "so clever, my dear, he didn't need to examine me, he just *knew* what to give" is ended. Bad service in any respect leads to a declining list, and in this respect the G.P. is far more vulnerable than the specialist, whose nearest rival may be many miles away.

The doctor–patient relationship is a peculiar and intimate one which must not be disrupted by the establishment of these divisions and compartments which our masters seem to seek for us. Of course the G.P. must continue to do midwifery. Pregnancy, parturition, and puerperium are times when his knowledge of family circumstances are of the greatest value, when the fact that he is by way of being a friend of the family is of tremendous help to all concerned. It is the very basis of good general practice, and already there has been too much of the idea that the doctor is less worthy than the midwife to help in this family event. The ever-improving maternity and child health figures must mean something, and it is hard to believe that the mortality rates for mothers and infants have continued to decrease in spite of the G.P. Much of the antenatal work done under the public health authorities is wasted, since the G.P., uninformed of what has transpired at the clinic, is called in to cope with whatever emergency arises. How much better, then, would the results be if there could be a little less quibbling and a little more co-operation.

As the basis of a good National Health Service it must be agreed by all sides that good G.P. work is the most important factor, with full access for the G.P. to all methods of investigation and treatment and all ancillary services. The G.P. is not the servant of the specialist and the administrator; they are there but to serve the patient, and that service is normally given through the G.P. Not only does the tail try to wag the dog just now, but it barks pretty freely as well. The following points clarify the situation.

1. A big list makes it hard to preserve full efficiency.
2. Smaller lists call for larger remuneration—the greatest single step towards 100% G.P. efficiency would be a largely increased capitation fee with a limitation of lists well below 4,000.
3. G.P. hospitals help to keep the G.P. up to his job and provide him with the extra diagnostic aids promised, but not yet forthcoming, in connexion with the health centres.
4. Antenatal work, with the district midwife, is properly the work of the family doctor.
5. The attention of school medical officers should be drawn to the fact that they are supposed to work with, not against, the G.P.

The extra disciplinary powers for Council, hidden away in the *Journal* of April 22 (*Supplement*, p. 149), will not in any way ease the problem, and one can only assume that the powers of the B.M.A. have also decided that the doctor is a bit of a shocker and in need of the added stimulus of the big whip. Perhaps both our advisers and our administrators might be persuaded that the average G.P. is not the incompetent, lazy, overpaid, underworked, unethical fellow, bluffing his way through life—with his bedside "veneer" and the hope of natural cure to help him over his difficulties—who appears to be pictured ever more frequently in your correspondence.—I am, etc.,

Spilsby, Lincs. C. E. FRISKNEY.

SIR,—I have read Dr. E. Anthony's letter (May 6, p. 1077), and my experience, I am glad to say, differs from his. Had Dr. Anthony the authority of his Division to sign his letter in his official capacity? My two partners and I do not find the patients more aggravating; the doctor–patient relationship is in no way impaired. We do not find "that it is a question of doing the bare minimum for everybody" and would be ashamed to admit it if it were true. We have no difficulty in getting patients into hospital. Our patients treat us with courtesy and consideration and are grateful for what is done for them. If you treat them fairly they will treat you fairly.

There are many improvements we could suggest, the first being the exhibition of good will by all doctors. How can we expect to enlist public sympathy when we are always crying out and abusing our patients? The Collings report is most disturbing, because it paints a vivid and accurate picture of only too many G.P.s. Let us put our own house in order if we wish to be listened to by a Ministry (of whatever party) which is only too aware of our very real shortcomings.

All surgeries should be inspected by a purely medical committee, and those that are inadequate should be penalized at once. It is grossly unfair that a man with adequate surgery accommodation and equipment should be paid the same capitation fee as one whose surgery betrays his meanness from both the financial and the professional aspects.—I am, etc.,

Walthamstow, E.17. ST. GEORGE B. DELISLE GRAY.

Hodgkin's Disease and Pregnancy

SIR,—In support of Dr. B. Jolles's opinion (May 13, p. 1142) that pregnancy does not necessarily mean exacerbation of Hodgkin's disease, may I put on record the following two cases?

A woman, aged 33, was seen in May, 1946, with six months' enlargement of glands in the left neck, which were partially removed and showed the histological features of Hodgkin's disease. There was no evidence of other enlarged glands and the chest radiograph was normal. The patient was treated in May and June, 1946, over the left cervical and mediastinal areas. She was kept under close observation, and in May, 1947, enlargement of the left axilla demanded treatment by irradiation. In May, 1948, there was an area of induration in the left breast which was regarded as due to Hodgkin's disease and which disappeared on irradiation. In February, 1949, the patient was delivered of a normal baby and has remained well ever since, with no clinically active disease in the nature of glandular enlargements or constitutional symptoms.

The second patient was aged 25, and was seen in hospital in September, 1933, with glandular enlargement in the left neck, which showed the histological features of Hodgkin's disease. Glandular recurrences in the left neck were treated by *x* rays in 1933, 1934, and 1935. The patient was delivered of twins in February, 1936, and another child was born in March, 1944. No evidence of Hodgkin's disease was noted on frequent follow-up visits until left axillary and cervical masses became noticeable in July, 1946, both of which reacted well to irradiation, and there has been no further trouble to date.

It is felt that the decision about termination of pregnancy has to be made in each case on its own merits, and it should certainly be considered in cases where the constitutional or local effects of Hodgkin's disease are not under control. In some centres even early cases of Hodgkin's disease are subjected to treatment by nitrogen mustard and allied drugs, and it has to be remembered that these will produce sterilizing effects on ovaries and testicles. These effects must be borne in mind before treating younger men or women.—I am, etc.,

London, W.2. M. HULBERT.

Kidnapped Greek Children

SIR,—Dr. Judith Waterlow (April 22, p. 963) repeats the familiar refrain about the Greek children being "evacuated" by the nice, kind Communist guerrillas in order that they might be spared the horrors of Monarcho-Fascist bombing. I am surprised and shocked that she should so completely lend herself to this Communist campaign as to repeat statements which she should know to be untrue. I refer primarily to her remarks about the United Nations Special Committee on the Balkans (Unscob). Dr. Waterlow would have your readers believe that Unscob found no evidence of forcible abductions. Now it is quite easy to check this assertion by consulting the two reports issued by Unscob which are obtainable from H.M. Stationery Office and which contain evidence collected on the spot by observer groups sent to the frontier areas to investigate this matter. You have already published a letter from Dr. D. S. Piper (May 13, p. 1143) giving extracts from one of these reports. I would like to add the following extract from the other report, which covers the period October 21, 1947, to June 16, 1948.

"One young woman told the group that on the morning of March 17 20 guerrillas entered her village (Vrisika) and took by force all the children under 18 years of age, some 180 persons. One child's arm was broken in trying to tear it away from its mother, and the child was left behind" (p. 30).

As for the glib assurance that the International Red Cross has testified to "the health and relative abundance which these children now enjoy in the various Eastern countries." Dr. Waterlow carefully omits to mention that the International Red Cross delegates were not even allowed to enter four of

the countries where abducted children are kept (Albania, Hungary, Poland, and Rumania). How on earth, then, could they have testified to the good treatment of the children in these countries? The answer is, of course, that they did not, for in the very report from which Dr. Waterlow quotes the International Red Cross states that its delegates were refused visas to visit these four countries. As for the other three countries to which, after repeated delays, the International Red Cross were eventually admitted, the report gives the number of the children visited. My methods of computation must be very different from those employed by Dr. Waterlow, for I make the total number visited 2,247, and not 28,000 as Dr. Waterlow suggests. She also discreetly ignores the following conclusion of the I.R.C. report:

"Whatever may have been the motives determining the evacuation of these children, whatever their living conditions may be in the reception countries, it nevertheless remains true that they are separated from their fathers and mothers and family homes, which nothing and no one can replace."

—I am, etc.,

S. L. HOURMOUZIOS,
Acting Director,
Greek Government Department of Information.

London, W.2.

*** This correspondence is now closed.—ED., *B.M.J.*

Gas-air Machines

SIR,—I have been greatly disappointed to find that the C.M. attachment to gas-air machines is not being extensively used. In 1936, Professor Chassar Moir at Oxford devised a method of giving relief from pain in labour from the inhalation of a limited quantity of pure nitrous oxide. He used a slow-filling gas bag fitted with facepiece and tubing, and the patient obtained about three breaths of pure gas with each pain.

In 1938, at the Wellhouse Hospital, Barnet, we combined this principle with the gas-air technique of R. J. Minnitt. The Dental Manufacturing Company made several experimental machines for our use whereby the patient obtained first two breaths of pure nitrous oxide and then continued with gas-air mixture. The principle is analogous to the priming device fitted to motor-cars for starting a cold engine. After the war the British Oxygen Company incorporated the idea in their new gas-air machine, describing it as the C.M. attachment.

The C.M. attachment consists of a slow-filling gas bag which plugs into the apparatus and is filled from a small by-pass. The apparatus was thoroughly tried out in Hertfordshire County Council hospitals, with most gratifying results. In 1949 the C.M. attachment was used in a large number of domiciliary confinements in certain districts of Hertfordshire by special arrangement with the Central Midwives Board and with the enthusiastic support of county general practitioners. The results were most carefully observed by the county medical officer of health, and these have led us to believe that this development of gas-air analgesia provides a technique whereby the mother can be definitely promised a painless labour in a normal confinement. It is very much to be hoped that other counties will follow the lead which Hertfordshire has given.

R. J. Minnitt, in the first publication of his work, particularly stressed that gas-air analgesia was not the end of our endeavours to help mothers, but only the first practical step on the road to complete relief from all pain in every confinement. Yet we have to-day an extraordinary attitude of complacency. There is a very general feeling that because gas-air has been made available for midwives' use no further effort need be made. In the official test carried out by the Royal College of Obstetricians and Gynaecologists it was found that 77% of mothers obtained adequate relief from pain by the inhalation of gas-air. We cannot be satisfied until 100% of all mothers are given the help they need.

Proper investigation should be made into all possible methods of giving relief from pain in labour, and there should be no further delay in testing, developing, and comparing on a national scale every drug and method of administration. In my opinion, regional hospital boards could have done a great deal more to help mothers.—I am, etc.,

JOHN ELAM.

New Barnet, Herts.

POINTS FROM LETTERS

Quality of Flour

Dr. HECTOR W. JORDAN (Mayfield, Sussex) writes: I was very glad to hear that Lord Sempill had drawn attention in the House of Lords to the fact that "the ideal loaf was made of compost-grown, stone-ground, 100% extraction flour" (Medical Notes in Parliament, May 6, p. 1084). Those who have tried this loaf have found that it has more flavour and is more satisfying than any other. Moreover, long experience has convinced me that those who change over to this kind of bread show a great improvement in their health. For the last 18 years I have been advocating a "whole-food" diet and have seen remarkable improvement in the health of all those who follow it; and even healthy people improve in fitness and endurance. . . .

Danger in the Cocktail Cabinet

Dr. S. GNESSEN (London, E.5) writes: The danger of young children gaining access to the cocktail cabinet was brought out last week when the young son (aged 6) of friends of mine drank two glasses of Benedictine and was admitted to hospital with acute alcoholism. Fortunately he came to no harm. In fact, he was very pleased with himself and said he liked the taste of it. Such an accident is not likely to occur very often, but it shows the importance of keeping the family drinks in a safe place.

Medical Evidence

Dr. OWEN L. RHYS (Cardiff) writes: In one case at a recent assizes the plaintiff had been an out-patient and an in-patient, and the medical witness had seen him in both instances and had given the patient and his doctor an opinion. The respondents some months later, without knowing that the hospital doctor had seen the plaintiff, had him examined by the same hospital doctor in private, and obtained a report similar to the one already given to the plaintiff's doctor. After evidence had been given the plaintiff's counsel accused the doctor of having broken his Hippocratic Oath. The judge made no comment. If this view is the correct one it would seem that that oath should read, "I will divulge nothing, unless it backs up the plaintiff's claim," and that the oath taken in court should be altered so that instead of the present "whole truth" it should say "such parts of the truth as will help to win my party's claim." . . .

The G.P. at the Crossroads

Dr. T. J. RYAN (London, N.W.1) writes: I think Dr. E. Anthony (May 6, p. 1077) deserves the thanks of all G.P.s in the London area in stating the facts. As a member of the B.M.A. for twenty years I would like to make the following suggestion: that the B.M.A. or some representative body bring out a small, attractive brochure—such as the London sub-postmasters' committee did some months ago—giving the facts of that letter, and that a copy be sent to every member of the House of Commons and the House of Lords and to all the principal newspapers, as the sub-postmasters did. . . . It will be up to the Press to bring to the notice of the public the true state of affairs. In his way we may get something done, and make the new Health Scheme an improvement on the old.

Identification of Tablets

Dr. W. J. PINOFF (Croydon) writes: Dr. A. B. Davies (April 22, p. 960) raises a point which for a long time has been puzzling me. As Dr. Davies rightly points out, colour and shape of tablets are not sufficiently distinct for identification. Neither does the inscription on the box "The Tablets" serve this or, for that matter, any useful purpose. . . . The remedy he suggests seems to me rather complicated, and not applicable to liquid medicines or powders, where the same danger of confusion exists. A much simpler and much more reliable solution of the whole problem would be to label the container, box, or bottle with a copy of the prescription. I know of at least one country on the Continent where this practice is a legal requirement, and it works excellently to the satisfaction of all concerned. There the chemist is obliged by law not to issue any substance without clearly stating on the container what it is, and his labels provide space for the copy of the prescription. . . . The present way of not stating on the container what it contains, except in a vague and obvious way, originated, I suppose, in the olden times when every doctor dispensed himself and did not want to reveal to outsiders, perhaps rivals, that his mysterious mixture did not contain more than a little sod. bicarb. But times have changed, and we no longer need the cloak of mystery to enhance our reputation.

Obituary

Dr. MARGARET JARVEY TROTTER died on May 5, at the age of 59. She graduated from Glasgow University in 1913, and until her marriage five years later she held the appointments of visiting physician to the Dispensary of the Royal Hospital for Sick Children, Glasgow, house-surgeon of the eye department, Glasgow Royal Infirmary, and assistant medical officer, Glasgow Education Authority. When there was a shortage of medical officers for clinics in London during the recent war, Dr. Trotter took up part-time service in Hackney at the antenatal and infant-welfare clinics. She did valuable work for over 25 years in the St. John Ambulance Brigade. She was a serving sister of the Order of St. John of Jerusalem, and recently received the long-service medal with bar. For many years she was on the committee of the Glasgow University Women's London Club, and was elected president in 1947 and vice-president in the two following years. Her interest in the nursing profession was maintained by work on the committee of the Royal British Nursing Association for over five years. She is survived by her husband, Dr. G. Clark Trotter, M.O.H. of Islington for 20 years, and by four daughters.—G. M.

Dr. DOUGLAS REGINALD PIKE died in London on May 6. A few weeks ago, in his seventy-fourth year, he was attending to his patients with the same whole-hearted and selfless devotion as at the beginning of his career forty-five years ago. Educated at Charterhouse, Oxford, and Guy's Hospital, he graduated M.B., B.Ch. in 1940, and since then had spent his life in general practice—first in London, then in a rural district of Lancashire, and for the last thirty years at Stevenage. He made it a rule for himself, and for his partners, that any call for his services at any hour of the day or night must be answered with the least possible delay. He had a large private and panel practice, and his failure to discriminate between the payers and the non-payers was at first alarming to his partners—until they acquired the same habit themselves. For him there were no short cuts in treatment and no economies in the prescription of drugs; if a patient needed something he could not afford, the firm supplied it without a thought of the cost. In obstetrics he had a reputation extending far beyond his own practice; had he devoted himself, as he originally intended, solely to this branch of medicine, his fame and his income would have been greatly increased. In principle, he was in favour of the State medical service, but the maintenance, under the new regime, of his extremely high standards of medical practice is doubtful, and it is perhaps fortunate for him that he did not live to see either the frustration of his lifelong objectives or the boredom of retirement. Like other single-minded men of his profession, he had few outside interests, and much of his scanty leisure was spent in keeping in touch with the latest developments in medicine. He was away from his practice for four years during the first world war, when he served with the R.A.M.C. in France and in India. He also found time much later for B.M.A. work. He was president of the Hertfordshire Division from 1942 to 1945, and during the last year of this period Dr. Pike was also chairman of the East Herts Division. He was a remarkable compound of Trollope's Doctor Thorne and the products of Lord Nuffield's beneficence a hundred years later. The letters written to his widow and children have shown that he was regarded by most of his patients rather as a friend and counsellor than as a doctor.—C. J. P. G.

Mr. ROBERT DEVEREUX MOTHERSOLE, who died on May 12 in his 85th year, was chairman of the Bolton Division of the British Medical Association from 1922 to 1926, and again from 1928 to 1934. He was president of the Lancashire and Cheshire Branch in 1932–3, and he represented his constituency at the Annual Representative Meetings from 1920 to 1932.

D. G. writes: Dr. Mothersole settled in Bolton in 1892. He soon joined the staff of the Bolton Infirmary (now the Royal Infirmary), and to him fell the task of introducing the new aseptic surgery to the hospital. This he did with tact and energy. He had an original mind, and his judgments were invariably sound; in committee work he was a tower of strength. As a surgeon he built up a high reputation. Later in life he took an interest in civic affairs at Bolton, and was a member and alderman of the town council. He will be remembered for a long time in the district for his professional work, as a kindly and sympathetic man.

J. M. writes: The sudden death of Dr. B. A. I. Peters came as a great shock to his many friends (May 27, p. 1274). From his school days Dr. Peters was immensely interested in chemistry, and he carried this interest with him throughout his life. In consequence he applied a wealth of biochemical knowledge to medical problems and wrote many articles from a biochemical point of view. His knowledge in this respect was far and away above the heads of the average medical man, and often, in his enthusiasm, Dr. Peters assumed knowledge in others which did not necessarily exist. For many years he was a member of the Biochemical Society. Living during the greatest period of advance in the treatment of infectious diseases, Dr. Peters approached all the problems with scientific care and, being always willing to apply experimental tests, produced many useful additions to the literature on the subjects of diphtheria, scarlet fever, gastro-enteritis, erysipelas, and immunization. He was a member of the Medical Research Council Committee on Cross Infections in Hospital, and, with his experience, was able to contribute sound, practical views. As a man, Dr. Peters was consistently upright throughout his life. He served his country during the 1914–18 war. He was a friend of children and took the greatest pleasure in their company; with adults he tended to be shy, but his friendship, once gained, was something to depend on and to be valued. Dr. Peters hated the spectacular, and his modesty in itself made him a great man. He belonged to the race of great clinical teachers, and his knowledge of humanity, medicine, biochemistry, birds, and flowers can ill be spared. Dr. Peters had become an institution, so benevolent and wise, that it is unbelievable that his advice is no longer available.

Dr. Bernard Myers writes: Although it was known that the health of Dr. Porritt had not been satisfactory for some time the news of the passing of an old friend, whom I had known for over fifty years, came as a shock (May 20, p. 1208). I can speak from personal knowledge of the fine service rendered by him as registrar and later as chief medical officer in the New Zealand hospital ship *Maheno* during the first world war. Of his many interests, he performed a great service to New Zealand in his indefatigable work in the cause of the preservation of the forests and birds of the Dominion. He foresaw how easily erosion occurs when a forest is ruthlessly destroyed, and the subsequent loss of crops and bird-life, and effect on the rainfall. He tried hard to prevent the introduction into New Zealand of animal pests which did such great damage in destroying the fauna and flora wherever the pests were most unwisely let loose. Ernest Porritt will be remembered by those who had the good fortune to know him as a good friend with charm of manner. Of him it could be said that he was a great gentleman.

Medical Notes in Parliament

Certificates from Unregistered Practitioners

Mr. READER HARRIS asked the Minister of National Insurance on May 23 about a directive to branch offices instructing them that a claim might be made for sickness benefit by furnishing certificates signed by a person other than a registered medical practitioner, such as an osteopath, Christian Science healer, or dentist. He asked how many sickness claims had been paid on the evidence of certificates issued by persons other than registered medical practitioners.

Dr. EDITH SUMMERSKILL replied that the National Insurance (Medical Certification) Regulations, 1948, required all claimants

for sickness benefit to submit evidence of their incapacity, and that, while this evidence normally included a medical certificate, the statutory adjudicating authorities could take into consideration alternative evidence of incapacity if they thought fit. She said that the information asked for in the last part of the question was not available, but that the numbers were believed to be very small.

Mr. HARRIS then asked whether the Minister was satisfied that certificates should be accepted from faith-healers, herbalists, and other persons over whom control might necessarily be very vague, and whether she herself, as a registered medical practitioner, was satisfied with a state of affairs whereby the Willesden Institute of Natural Healing could tout for business by issuing circulars which stated that certificates were available for National Insurance purposes.

Dr. SUMMERSKILL pointed out that this method of determining incapacity had been operating for nearly forty years, and added that if Mr. Harris were a little older he would remember the sect called the "Peculiar People" who had a religious objection to doctors, and who had, in fact, formed their own approved society. She was quite aware of the fact that this right which people had of exercising conscientious objection, and which they all believed it was right for them to have, might be abused, but she assured Mr. Harris that the Government were keeping a careful eye on the matter and that they had certain safeguards such as sick visitors and regional medical officers who could be called in for further medical examinations.

Mr. HARRIS then asked whether the Minister drew some distinction between public funds and the funds of an approved society which had not before been public funds.

Dr. SUMMERSKILL said that Mr. Harris was displaying appalling ignorance and asked whether he did not know that, before 1948, these approved societies had used both public funds and private funds.

Mr. EWART then asked whether Dr. Summerskill was aware that her reply would give great satisfaction to thousands of people in this country who had for many years exercised this right of freedom of choice in determining what type of treatment they should take when sick.

Architects.—Dr. CHARLES HILL asked the Minister of Health on May 18 the number of architects and architectural staff employed by the North West Metropolitan Regional Hospital Board. Mr. BEVAN replied that the architect's department for the board included 47 professional and technical officers, of whom 24 were architects and architectural staff.

Inventories.—Dr. CHARLES HILL also asked the Minister of Health the total estimated annual cost of putting into effect his circulars R.H.B. (50) 17, H.M.C. (50) 17, B.G. (50) 15, requiring hospital authorities to prepare inventories in a prescribed form; and the total estimated annual saving in public money as a result of taking such inventories. Mr. BEVAN answered that he did not think any useful estimate was possible under either heading.

Medico-Legal

AN INJUSTICE RIGHTED

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

In passing the Matrimonial Causes Act, 1937, often referred to as Herbert's Act, the legislature made some far-reaching reforms in the law of nullity. A degree of nullity may now be pronounced, *inter alia*, on proof that, at the time of the marriage and unknown to the petitioner, the respondent was insane or suffering from venereal disease. Hence for the first time there was a distinct possibility that there might be a child of the marriage conceived after the ceremony. In order to avoid bastardizing such a child Parliament enacted that, where a marriage was annulled on these grounds, a child of the marriage should remain legitimate. It did not protect a child conceived before the marriage, nor (for the possibility did not then arise) one conceived after the marriage by artificial insemination. A few years ago the courts decided that in either of these cases[1,2] the child became illegitimate on the issue of the decree, which operated retrospectively.

This result was obviously unfair to the child, and so last year Parliament passed the Law Reform (Miscellaneous Provisions) Act, 1949, which provided among other things that, where a decree of nullity is granted in respect of a voidable marriage (one otherwise valid), any child who would have been a legitimate child of the parties to the marriage if it had been dissolved (by divorce) instead of being annulled shall on the date of the decree be deemed to be their legitimate child notwithstanding the annulment. The effect of this is that the child will now remain legitimate if the marriage is voidable.

A learned commentator[3] suggests in *Law Notes* that a similar result will follow if the child has been legitimated by the subsequent marriage of its parents, which, under Section 1 of the Legitimacy Act, 1926, makes the child legitimate as from the date of the marriage. In any case the disadvantage of illegitimacy, which the legislature could not have intended to inflict, will not now attach to a child conceived before an annulled marriage, or during it as a result of artificial insemination, at any rate by the husband's semen.

[1] *Dredge* v. *Dredge* (1947), 63, T.L.R. 113.
[2] *R. E. L.* v. *E. L.*, *British Medical Journal*, 1948, **2**, 1086.
[3] *Law Notes*, 1950, **69**, 39.

Universities and Colleges

UNIVERSITY OF EDINBURGH

Dr. Daniel Bovet, D.Sc., director of the Istituto Superiore di Sanita, Rome, who was awarded the Cameron Prize of 1949, will deliver a lecture on "The Discovery of Antihistamines" in the anatomy lecture theatre, University New Buildings, Edinburgh, on Tuesday, June 6, at 5 p.m. Students and graduates are invited to attend the lecture.

A lecture on "The Hormones of the Anterior Hypophysis" will be delivered by Dr. Herbert M. Evans, director of the Institute of Experimental Biology, University of California, in the anatomy lecture theatre, University New Buildings, Edinburgh, on Wednesday, June 7, at 5 p.m. Senior students and graduates in medicine are invited to attend the lecture.

UNIVERSITY OF DURHAM

Dr. G. M. Trevelyan, O.M., F.R.S., was installed as Chancellor of the University of Durham on May 24, when he conferred a number of honorary degrees, including that of D.Sc., on Professor E. D. Adrian, O.M., M.D., F.R.C.P., F.R.S., Professor of Physiology in the University of Cambridge.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At the annual general meeting of the College, held on May 20, with the President, Professor Hilda Lloyd, in the chair, the following were elected to the Council to fill statutory and other vacancies: *As representatives of the Fellows*, D. Baird, W. E. Barnie-Adshead, A. M. Claye, V. Lack, G. I. Strachan, R. C. Thomas. *As representatives of the Members*, A. M. Sutherland, S. A. Way. In addition to those elected the following were co-opted for the ensuing year: W. A. G. Bauld, Sir William Gilliatt, C. D. Read, B. H. Swift, L. Williams.

The President was appointed to represent the College at the 150th anniversary celebrations of the Royal College of Surgeons of England.

The following were admitted to the Fellowship: H. G. E. Arthure, Elinor F. E. Black, J. H. Boyd, R. Everett, P. J. Ganner, Kathleen M. D. Harding, F. J. Hayden, K. A. K. Hudson, T. I. Hughes, B. L. Jeaffreson, R. W. Knowlton, Joyce Morgan, J. S. Quin, D. A. O'C. Quinlan, L. M. Snaith, G. R. Stoneham, Margaret M. White.

The following were admitted to the Membership: J. A. Bentham, D. W. Briggs, H. McK. Carey, Florence J. G. Chouler, R. Crawford, R. Cutts, M. S. Ellensweig, H. J. Fisher, Elizabeth M. Harper, W. F. Harper, J. S. Hesketh, P. Kalyanikutty, J. A. Love, Sarah Macaskill, A. S. Majury, A. T. Marshall, J. D. Martin, J. G. Napier, F. P. Pigott, J. H. McK. Pinkerton, C. C. Pretorius, S. Rajanayagam, T. M. Roulston, J. H. Routledge, A. C. Sinha, Z. H. Y. Sobani, W. A. Souter, A. Starritt, G. Winchester.

No. 19

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended May 13.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1950 (a)	(b)	(c)	(d)	(e)	1949 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Meningococcal infection	37	5	28	1	—	21	2	20	2	1
Deaths		—	—				—	2		
Diphtheria	43	2	12	2	3	87	5	31	1	13
Deaths	—	—	—	—	—	3	—	—	—	—
Dysentery	444	15	103	3	1	59	10	41	—	—
Deaths					—				—	—
Encephalitis, acute	3	—	—		—	2	—	1	—	—
Deaths		—		—			1			
Erysipelas			22	9	7	*		18	5	5
Deaths										
Infective enteritis or diarrhoea under 2 years				20					58	
Deaths	17		6	1	—	21	—	5	4	2
Measles*	7,278	262	656	209	260	9,217	1170	460	227	169
Deaths†			2	—	1			—	3	—
Ophthalmia neonatorum	31	3	9		—	47	2	9	—	2
Deaths										
Paratyphoid fever	11	—	—		—	3	—	2(B)	—	1
Deaths	—		—		—	—	—	—	—	—
Pneumonia, influenzal	502	12	7	—	7	494	24	8	12	7
Deaths (from influenza)‡	17	2	1	3	—	25	—	2	2	—
Pneumonia, primary			190	¶				159		
Deaths	169	26		15	5	153	22		7	5
Poliomyelitis, acute	22	1	5	2	5	14	2	4	1	—
Deaths§	2	—		—		1	—			
Puerperal fever		—	7				—	10		
Deaths										
Puerperal pyrexia‖	80	3	11		2	91	8	3	—	—
Deaths							—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,322	98	168	83	80	898	63	126	67	34
Deaths†			—	—	—			—	—	—
Smallpox	—	—	—		—	—	—	—	—	—
Deaths					—				—	—
Typhoid fever	6	—	—	4	1	37	—	2	—	—
Deaths	—	—	—		—	1	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths					—				—	—
Whooping-cough	3,469	203	386	131	59	3,053	196	229	123	76
Deaths	2	1	—	—	—	3	1	1	5	—
Deaths (0–1 year)	249	33	36	19	13	259	32	39	25	17
Deaths (excluding stillbirths)	4,757	754	588	168	123	4,537	699	599	181	124
Annual death rate (per 1,000 persons living)			11·8					12·0	11·2	
Live births	7,875	1282	999	366	246	8,188	1264	1017	484	274
Annual rate per 1,000 persons living			20·1					20·4	30·0	
Stillbirths	200	23	21			218	26	33		
Rate per 1,000 total births (including stillborn)			21					31		

* Measles is not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

¶ Primary pneumonia no longer notifiable in Eire.

EPIDEMIOLOGICAL NOTES

Discussion of Table

In *England and Wales* infectious diseases were more prevalent and rises were recorded in the notifications of measles 961, whooping-cough 240, dysentery 103, and scarlet fever 55, the only fall of any size being acute pneumonia 32.

The largest rises in measles notifications were Lancashire 146, Middlesex 134, London 121, Yorkshire West Riding 111, and Norfolk 102. No large variations occurred in the local trends of scarlet fever. The only notable variation in the returns of diphtheria was a decrease of 4 in Durham. The largest increases in whooping-cough were Yorkshire West Riding 79, Essex 43, and London 36.

Dysentery increased, particularly in Lancashire, where the notifications were 70 more than in the preceding week. The largest returns were Lancashire 142 (Manchester C.B. 68, Preston C.B. 34, Failsworth U.D. 13, Chadderton U.D. 9); Yorkshire West Riding 103 (Bradford C.B. 40, Sheffield C.B 28); Durham 63 (Stanley U.D. 20, South Shields C.B. 14); Surrey 20 (Sutton and Cheam M.B. 18); Northumberland 18 (Newcastle-upon-Tyne C.B. 12); Yorkshire North Riding 16 (Middlesbrough C.B. 15); London 15; and Gloucestershire (Cheltenham M.B. 7).

In *Scotland* the rises in the number of notifications included measles 189, whooping-cough 65, acute primary pneumonia 34, dysentery 14, and cerebrospinal fever 10. Dysentery was notified chiefly in Glasgow 56, Dundee 18, and Edinburgh 13. The increased incidence of cerebrospinal fever and measles was mainly contributed by Glasgow, and the rise in whooping-cough and acute primary pneumonia was common to the whole country.

In *Eire* an increase was reported in the notifications of whooping-cough 67 and measles 62. The increases were due mainly to two outbreaks—Meath (Dunshaughlin R.D. 35) and Dublin (Dublin South R.D. 17); the rise in measles was fairly general throughout the country.

In *Northern Ireland* increases were recorded for measles 22, whooping-cough 10, and scarlet fever 9. In Belfast C.B. an increase of 31 occurred in the number of notifications of measles.

Quarterly Returns for Eire

During the December quarter the birth rate was 19.4 per 1,000, 0.6 below the rate for the fourth quarter of 1948. The infant mortality was 58 per 1,000 births, 10 above the rate for the preceding December quarter. The general death rate was 12.1 per 1,000, 0.7 above the rate for the preceding fourth quarter. Deaths from diarrhoea and enteritis numbered 172, compared with 82 in the fourth quarter of 1948. Of the remaining 36 deaths from the principal epidemic diseases 21 were attributed to whooping-cough. Deaths from pulmonary tuberculosis were 420 and from other forms of tuberculosis 96. These were 72 and 42 respectively below the numbers of the preceding fourth quarter.

For the whole year the birth rate was 21.4 per 1,000, 0.5 below the rate for 1948. The infant mortality was 51 per 1,000 registered births, 2 above the rate for 1948. The general death rate was 12.7 per 1,000 and was 0.5 above the rate for the preceding year. There were 702 deaths attributed to the principal epidemic diseases, and these deaths included 483 from diarrhoea and enteritis, 131 from whooping-cough, 53 from measles, 12 from typhoid fever, 11 from scarlet fever, and 10 from diphtheria. There were 2,111 deaths registered from pulmonary tuberculosis and 540 from other forms of tuberculosis; these totals were 287 and 79 below the totals of 1948.

Week Ending May 20

The returns of infectious diseases in England and Wales during the week included: scarlet fever 1,177, whooping-cough 3,237, diphtheria 51, measles 8,828, acute pneumonia 594, acute poliomyelitis 25, dysentery 391, paratyphoid fever 13, and typhoid fever 7.

Medical News

Protection of Overseas Practitioners

Probably most medical practitioners who come from overseas to Britain for postgraduate study become members of one of the medical defence societies for the period of their residence in this country. Certainly they would be well advised to do so. But probably few know that legal actions can be brought against them long after they have returned to their home countries, by which time membership may have lapsed. A surgeon, for example, may have a claim laid against him as the result of an operation performed any time up to six years previously. The defence societies have made special provisions to cover such possibilities for visitors from overseas, and particulars may be obtained from the secretaries of them. Their addresses are as follows: Medical Defence Union, 49, Bedford Square, London, W.C.1; Medical Protection Society, Victory House, Leicester Square, London, W.C.2.

Training of Laboratory Technicians

The City and Guilds of London Institute has adopted new regulations and syllabuses for the Laboratory Technicians' Intermediate Certificate Examination, under which the first examination will be held in May, 1951. The scheme has been drawn up by the Institute's Advisory Committee on Laboratory Technicians' Work. Syllabuses for the Final Certificate Examination are being prepared. The scheme is intended to meet the requirements of laboratory technicians in schools, technical colleges, universities, industrial organizations, and research associations. In drawing up the new scheme the Advisory Committee had before it a number of aims, including the following:

(i) The primary objective should be to train first-class, practically competent laboratory technicians.

(ii) The education and training, particularly in the earlier stages, should be on a broad basis, with opportunity for the development of students' general education.

(iii) To maintain students' interest and in pursuance of the primary objective, there should be opportunity for students to do specialized work related to the type of laboratory in which they are employed.

(iv) The training should permit of a measure of mobility for technicians wishing to move from one type of laboratory to another.

(v) As the intention is to provide a comprehensive and nationally recognized qualification, the structure of the scheme should make allowance for flexibility in instruction and in the number of specialized subjects catered for.

(vi) That the standard required should be such that the certificate will achieve wide recognition and make a contribution towards the improvement of the efficiency and status of the science laboratory technician.

It is expected that candidates for the examination will normally come forward after satisfactory completion of a course of study either at a technical college or at their place of employment (e.g., university department or industrial organization), or at a course provided partly at a technical college and partly at the place of employment. Provision is also made for the entry of external candidates. The course of part-time instruction proposed is of three years' duration.

Manchester Golf

The annual competition of the Manchester and District Medical Golfers' Association was held on the course at Mere, Cheshire, on May 17. There were 88 competitors. The Challenge Cup was won by Dr. L. K. Hughes (Manchester) with a net score of 69. The Captain's second prize was awarded to Dr. J. D. Gallagher (Atherton) with a net return of 70. Dr. J. Walker (Manchester) received the Walter Gold Medal for the best gross score of 76, and the Walter Silver Medal was won by Dr. G. B. Hardman (Manchester) for the best gross score of 83 from among those with handicaps of ten and upwards. Club prizes were also won by Dr. I. R. Duthie (Blackburn) and Dr. G. G. Mowat (Bolton).

Growth of Infants and Young Children

The Ministries of Health and Education, in conjunction with the British Paediatric Association, is undertaking a survey of the growth of infants and young children in a number of areas in England and Wales. The survey, which began in 1949, is being made in selected child-welfare centres in Birmingham, Bristol, Cardiff, Finchley, Kent, Leeds, Liverpool, London, Northumberland, Norwich, and Rhondda. Dr. Ethel Cassie is supervising the field work on behalf of the Ministry of Health. It is hoped that in the first place about 20,000 babies (all of whom enter the survey below the age of two months) will be included and that the survey will continue for at least three years or longer, if possible. Records are being obtained of the mother's obstetric history, and the infant's birth and subsequent weights taken at regular intervals. The children are examined each time they attend the welfare centres; information is obtained on the type of feeding, and any illnesses occurring between the visits are recorded. The height is measured from 18 months onwards. In addition, various social and economic data are being collected, including the father's occupation, whether or not the mother goes out to work, the size of the family to which the child belongs, housing conditions, and sleeping arrangements. These four sets of data will be examined so that their effect on each other can be determined. The committee organizing the survey under the chairmanship of Dr. J. E. A. Underwood, Ministry of Education, includes Dr. C. P. Pinckney and Dr. G. H. Newns, of the British Paediatric Association, Dr. Cecilie Asher, of the Ministry of Education, and Dr. H. E. Magee, Dr. Ethel Cassie, Dr. G. I. Brodie, and Dr. E. R. Bransby (who is also secretary) of the Ministry of Health. Assistance in the planning of the survey is being given by the staff of the Institute of Social Medicine, Oxford, by Dr. J. W. B. Douglas, Director of the Population Investigation Committee, and the Mathematics Division of the National Physical Laboratory.

Medical Mayor

Alderman Dr. G. H. Barendt was elected Mayor of Southampton on May 24. Dr. Barendt is the representative of the Southampton Division in the Representative Body of the B.M.A. and is a former chairman of the Division.

Nurses' Appeal

The Royal College of Nursing is appealing for £500,000 to pay for postgraduate training of nurses to enable them to become teachers and administrators.

Heberden Oration

The Heberden Oration on "The Rheumatic Diseases as Diseases of Adaptation" will be delivered by Professor Hans Selye, of Montreal, before the Heberden Society at B.M.A. House, Tavistock Square, London, W.C., on Friday, June 2, at 5 p.m., and on Saturday, June 3, at 10 a.m.

COMING EVENTS

Criminal Psychopaths

The Institute for the Scientific Treatment of Delinquency and the Howard League for Penal Reform have arranged for a film on the Institute for Criminal Psychopaths, Herstedvester, Copenhagen, Denmark, to be introduced by Dr. Georg Stürup, medical director of the Herstedvester Institute, at the Institut Français du Royaume-Uni, Queensberry Place, London, S.W., on Tuesday, June 6, at 8.15 p.m. Sir Hartley Shawcross will take the chair and open the discussion.

British Medical Students Association

The following arrangements have been made for the week June 2 to 9. *Aberdeen* (Anatomical and Anthropological Society).—June 6: lecture on "Nutrition," by Dr. Howie, of the Rowett Research Institute. *Oxford University Medical Society.*—June 6: lecture on "Research in Radionics," by Mr. G. W. De La Warr, director of the Delawarr Laboratories.

Medicine and Surgery at Brussels

A series of lectures on different aspects of medicine and surgery—the Journées Médicales de Bruxelles—will be held in Brussels from June 10 to 18. Particulars may be obtained from Bruxelles-Médical, 141, Rue Belliard, Bruxelles.

Medical Photography

An International Exhibition of Medical Photography, sponsored by the Medical Group of the Royal Photographic Society, will be held at the Medical Society of London, 11, Chandos Street, W.1, on June 12 to 24 (10 a.m. to 5 p.m.; Wednesdays 10 a.m. to 8 p.m.). Sir Heneage Ogilvie, chairman of the Group, will open the exhibition at 4 p.m. on June 10.

Midwife Teachers Training College

Professor Hilda Lloyd, President of the Royal College of Obstetricians and Gynaecologists, will open the Midwife Teachers Training College, High Coombe, Warren Road, Kingston Hill, Surrey, on Thursday, June 15, at 3 p.m.

Scottish Medical Golfing Society

The summer meeting of the Scottish Medical Golfing Society has been arranged for June 24 and 25 at St. George's, Sandwich. The society is limited to sixty members, and a few vacancies exist. The qualification of the society is that members must be a graduate of a Scottish university or be of full Scottish parentage. Further particulars may be obtained from the honorary secretary, Mr. Norman Fleming, 2, Park Square West, London, N.W.1.

Industrial Health

The third Mackenzie Industrial Health Lecture, given under the auspices of the B.M.A. in conjunction with the Association of Industrial Medical Officers, will be delivered by Professor R. E. Lane on Wednesday, June 28, at 2.30 p.m. in the Main Hall, Nuffield House, Queen Elizabeth Hospital, Birmingham. His subject is "Education and Industrial Health." Admission is free.

Congress of Radiology

The Sixth International Congress of Radiology will be held in London during the week July 24–29 under the presidency of Dr. Ralston Paterson. The International Committee will meet on Sunday, July 23. Demonstrations will be given during the week preceding the congress and the two weeks after it. Information may be obtained from the secretary of the congress at 45, Lincoln's Inn Fields, London, W.C.2.

SOCIETIES AND LECTURES

A fee is charged for attending lectures marked ●. Application should be made first to the institution concerned.

Friday

HEBERDEN SOCIETY.—At B.M.A. House, Tavistock Square, London, W.C., June 2, 5 p.m., *"The Rheumatic Diseases as Diseases of Adaptation,"* Heberden Oration by Professor Hans Selye (Montreal). (See Saturday also.) (*Corrected time.*)

Saturday

HEBERDEN SOCIETY.—At B.M.A. House, Tavistock Square, London, W.C., June 3, 10 a.m., *"The Rheumatic Diseases as Diseases of Adaptation,"* Heberden Oration by Professor Hans Selye (Montreal). (See Friday also.)

Monday

EDINBURGH UNIVERSITY.—At Physiology Lecture Theatre, University New Buildings, Teviot Place, June 5, 5 p.m., *"Teacher and Student in Medical Education,"* by Dr. Douglas Guthrie.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—June 5, 5.30 p.m., *"The Problem of Awareness and Non-awareness of Visual Field Defects,"* by Dr. Macdonald Critchley.

ROYAL EYE HOSPITAL, St. George's Circus, London, S.E.—June 5, 5 p.m., *"Ocular Complications of Diabetes,"* by Dr. T. H. Whittington.

UNIVERSITY COLLEGE (Physiology Theatre), Gower Street, London, W.C.—June 5, 4.45 p.m., *"Genetics and Biochemistry,"* by Professor J. B. S. Haldane, F.R.S.

Tuesday

EDINBURGH UNIVERSITY.—At University New Buildings (Anatomy Lecture Theatre), Edinburgh, June 6, 5 p.m., *"The Discovery of Antihistamines,"* by Dr. Daniel Bovet, D.Sc. (Rome).

INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—June 6, 5 p.m., *"Pigmentary Conditions of the Skin,"* by Dr. I. Muende.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—June 6, 5 p.m., *"The Anatomy and Physiology of the Spleen,"* Arnott Demonstration by Mr. F. S. Gorrill.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School, Paddington, W.—June 6, 5 p.m., *"The New Genetics,"* by Dr. C. D. Darlington, F.R.S.

Wednesday

EDINBURGH UNIVERSITY.—At University New Buildings (Anatomy Lecture Theatre), Edinburgh, June 7, 5 p.m., *"The Hormones of the Anterior Hypophysis,"* by Dr. Herbert M. Evans (University of California).

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—June 7, 5.30 p.m., *"Electroretinography,"* by Dr. K. Tansley.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—June 7, 4.30 p.m., lecture-demonstration for post-graduates by Dr. E. Stengel.

ROYAL EYE HOSPITAL, St. George's Circus, London, S.E.—June 7, 5.30 p.m., *"Skin Diseases and the Eye,"* by Mr. L. H. Savin.

WEST LONDON HOSPITAL MEDICAL SCHOOL, Wolverton Gardens, Hammersmith, W.—June 7, 8.30 p.m., *"The Surgery of the Sympathetic Nervous System,"* Third Alex. Simpson-Smith Memorial Lecture by Sir James Learmonth.

Thursday

HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, June 8, 5 p.m., *"Drug Rashes,"* by Dr. G. A. Grant Peterkin.

INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—June 8, 5 p.m., *"Lupus Erythematosus,"* by Dr. H. Gordon.

INSTITUTE OF NEUROLOGY: NATIONAL HOSPITAL, Queen Square, London, W.C.—June 8, 5 p.m., *"Combined Neurovascular Lesions of the Extremities,"* by Sir James Learmonth.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—June 8, 2.30 p.m., visit to Glaxo Laboratories.

LONDON UNIVERSITY.—At King's College, Strand, W.C., June 8, 5.30 p.m., *"The Development of Normal and Abnormal Vision Observed in Animals with Transplanted Eyes,"* by Professor L. S. Stone (Yale University).

ROYAL EYE HOSPITAL, St. George's Circus, London, S.E.—June 8, (1) 4.15 p.m., *"Methods of Examination,"* by Mr. C. M. Shafto; (2) 5 p.m., *"Papilloedema and Optic Neuritis,"* by Dr. S. Nevin.

Friday

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—June 9, 5.30 p.m., *"The Pathology of Exudative Uveitis,"* by Mr. E. Wolff.

MAIDA VALE HOSPITAL FOR NERVOUS DISEASES MEDICAL SCHOOL, Maida Vale, London, W.—June 9, 5 p.m., clinical neurological demonstration, by Dr. Samuel Nevin.

ROYAL SANITARY INSTITUTE.—At Town Hall, Wallasey, Cheshire, June 9, 10.30 a.m., Papers: *"Some Aspects of Sanitary Administration in a Holiday Resort,"* by Mr. W. Bate, D.P.A.; *"Co-ordination of the Work of the Sanitary Inspector and the Borough Surveyor,"* by Mr. H. Crowther, M.Eng., A.M.I.C.E. Afternoon: visits will be made.

BIRTHS, MARRIAGES, AND DEATHS

BIRTH

Edwards.—On May 18, 1950, at West Didsbury, Manchester, to Judy, wife of Dr. J. Edwards, a son.

MARRIAGES

Davies—Whiteaway.—On April 15, 1950, at St. Peter's Church, Hersham, Leslie William Davies, M.B., B.S., D.O.M.S., of Teddington, Middlesex, to Mary Angela Whiteaway, of Weybridge, Surrey.

Dux—Norton.—On May 21, 1950, in London, Eric F. W. Dux, M.Sc., A.R.I.C., to Margot S. Norton, M.B., B.S.

DEATHS

Brown.—On May 21, 1950, at the Royal Infirmary, Edinburgh, Donald Thomas Alexander Brown, M.S., F.R.C.S.Ed., of Newbury, Berks, aged 28.

Brown.—On May 23, 1950, at Charing Cross Hospital, London, W.C., Leonard Graham Brown, M.C., D.M., F.R.C.S., of 82, Portland Place, London, W., aged 62.

Clark.—On May 24, 1950, at Gerrards Cross, Lizzie Mackay Smith Clark, M.B., Ch.B., of Cromer, Bulstrode Way, Gerrards Cross, Bucks.

Coleman.—On May 21, 1950, James Jordan Coleman, M.B., late of Sheffield and Bridlington.

Little.—On March 12, 1950, at Mossview, Newmains, Lanarkshire, John Watson Little, sen., M.B., Ch.B.

Moodie.—On May 23, 1950, at 3, Cardigan Gardens, Goodmayes, Essex, David Moodie, L.R.C.P.&S.Ed., L.R.F.P.S.Glas., formerly of Bath.

Paterson.—On May 23, 1950, at 57, Marlborough Road, Ipswich, Arthur William Paterson, M.B., C.M., aged 79.

Snowden.—On May 20, 1950, at Bournemouth, Arthur de Winton Snowden, C.B.E., M.D., of 5, Grosvenor Road, Bournemouth, late of Linford, Ringwood, aged 77.

Townley.—On May 24, 1950, at 251, Seymour Grove, Manchester, Herbert Townley, M.B., Ch.B., B.D.S.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Primary Vaccination in Young Adults

Q.—*Are any special precautions necessary when vaccinating an unvaccinated girl of 21 against smallpox? What is the best method to use?*

A.—Primary vaccination in a young healthy adult is not likely to give rise to any untoward sequelae. Post-vaccinial encephalitis is a very rare but serious complication (the incidence is variously given as 1:10,000 to 1:100,000) which is particularly associated with late primary vaccination. Generalized vaccinia is another rare complication which occurs especially in persons with chronic skin infections, such as eczema. Care should be taken to control secondary septic infection of the vaccinated area—for example, by the use of penicillin cream—and, as the local reaction in a late primary vaccination may be severe, the patient should carry the arm in a sling from the fifth to the tenth day. If the person to be vaccinated is a contact of a case of smallpox, the quickest and perhaps most effective method to use is the single linear insertion with a Hagedorn needle through the lymph, but the method now ordinarily recommended is the multiple pressure technique described in the *Journal* of December 24, 1949 (p. 1483).

Thiocyanate Treatment of Hypertension

Q.—*What briefly is the dosage employed in the thiocyanate treatment of hypertension? Are there any contraindications?*

A.—Potassium thiocyanate may be given by mouth in initial doses of 2–3 gr. (0.13–0.2 g.) t.d.s. after meals. The serum thiocyanate must be measured on the seventh day and then at weekly intervals. Subsequent dosage may be regulated as follows:

Thiocyanate level	*Dosage recommended*
Under 5 mg.%	2–3 gr. (0.13–0.2 g.) t.d.s.
5–7 mg.%	1.5 gr. (0.1 g.) t.d.s.
7–10 mg.%	1 gr. (65 mg.) t.d.s.
Over 10 mg.%	Stop drug for one week.

The lowest blood level compatible with a satisfactory hypotensive effect should be maintained for three to six months. Further courses may be given as desired. Contraindications include senility, weakness and dizziness, and poor renal function. The drug is extremely toxic and should be administered with great care.

Tuberculosis in Infancy

Q.—*What is the incidence and what is the mortality of primary tuberculosis in each of the first three years of life?*

A.—All the available information on this point is given in the following tables. Table I shows first of all the distribution in 1946 and 1947, when the division was only into age groups 0–1 and 1–5, and then the figures for 1948 and 1949, when the form of notification was altered so as to provide also information about the age group 1–2. Table II shows the deaths and the death rates per million at ages 0–1 and 1–5 from respiratory, non-respiratory, and all forms of tuberculosis. The rates for 1948 and 1949 are all based on the 1947 population.

TABLE I.—*England and Wales: Formal Notifications of Tuberculosis at Ages 0–5*

	Respiratory				Non-respiratory			
Ages	0–1		1–5		0–1		1–5	
Year	Notifications	Rate per Million	Notifications	Rate per Million	Notifications	Rate per Million	Notifications	Rate per Million
1946	108	154	878	343	122	174	1,358	530
1947	181	208	1,113	455	134	154	1,338	547

Ages	0–1		1–2		2–5		0–1		1–2		2–5	
Year	Not.	Rate	Not.	Rate	Not.	Rate	Not.	Rate	Not.	Rate	Not.	Rate
1948	201	256	417	482	1,017	508	129	164	307	355	1,059	529
1949	169	238	377	500	1,122	501	89	126	278	369	949	424

TABLE II.—*England and Wales: Deaths and Death Rates from Tuberculosis at Ages 0–1 and 1–5*

	Respiratory				Non-respiratory				All Forms			
Ages	0–1		1–5		0–1		1–5		0–1		1–5	
Year	Deaths	Rate per Million	Deaths	Rate per Million	Deaths	Rate per Million	Deaths	Rate per Million	Deaths	Rate per Million	Deaths	Rate per Million
1946	72	103	136	53	212	302	720	281	284	405	856	334
1947	98	112	161	61	239	274	743	280	337	386	904	341
1948	77	88	120	45	169	194	669	253	246	282	789	298

Girdle Pain in Arthritis

Q.—*What is the treatment and what is the prognosis in a case in which severe girdle pain is due to pressure on the twelfth thoracic nerve following arthritic changes in the spine? The patient is a man of 71 and is not a good surgical risk.*

A.—Root pain associated with degenerative changes in the spine may often be relieved by wearing a suitable spinal support. As a temporary measure, a well-moulded plastic jacket is equally effective. As to the prognosis, degenerative changes, are, of course, permanent; but the root pressure symptoms tend to subside and the disability is not necessarily progressive. Operative treatment is seldom indicated in this type of case. It must be emphasized that caution is necessary in attributing girdle pains to osteoarthritis unless other causes can be eliminated. When severe deformity exists, as in patients with long-standing kyphoscoliosis, pressure on a nerve root due to structural changes and secondary arthritis is common enough, and the pain may be severe. But in simple arthritis without deformity any isolated girdle pain is seldom of severe degree. Other lesions that must be considered when a patient complains of severe root pain are prolapsed intervertebral disk; destructive bone infections; slipping rib cartilage; primary neoplasms, benign or malignant; and (particularly in old persons) metastatic deposits. A correct diagnosis can be reached only after consideration of a detailed history of the case, a complete neurological and orthopaedic examination, adequate radiography, and, when indicated, lumbar puncture and the appropriate laboratory tests.

Cold Agglutinins

Q.—*What is the significance of the finding of cold agglutinins in the serum which are not reversible at higher temperatures? The patient concerned suffered from glandular fever and subsequently suffered from what was presumably a virus pneumonia with a subsequent rise in the cold agglutinins (over 1 in 2,000). The patient has made a full clinical and radiological recovery from the pneumonia, but now shows cold agglutinins up to 1 in 2,000, and the reaction is irreversible.*

A.—The titre of cold agglutinins to red cell suspensions following an attack of virus pneumonia seldom exceeds 1 in 200 to 1 in 300 and disappears during convalescence. The high titre of agglutinins, unaffected by changes in temperature, described in this case suggests that some non-specific factor is responsible. Red cell suspensions that have become contaminated after standing for some hours may show auto-agglutination which is not prevented or reversed by rise of temperature, even up to 37° C. (Thomsen phenomenon). Again certain diphtheroids present as contaminants in serum may produce pan-agglutination of red cells. If these two factors can be ruled out, it may be necessary to find whether some rare iso-agglutinin is present in the patient's serum by testing the serum against red cell suspensions of different known human groups, including M and N.

Carcinoma of the Prostate

Q.—*A man of 61 had a small hard carcinoma of the prostate with a serum acid phosphatase of 38.5 units. On stilboestrol and iron his symptoms have disappeared. The prostate now feels normal, small and soft, and the serum acid phosphatase reading is 0.9 Gutman units. What is the prognosis in this case? Is it possible to say what is the expectation of life, and is it possible to give any idea of how such a case would end?*

A.—The immediate response of this patient with carcinoma of the prostate to stilboestrol therapy is satisfactory, and the improvement is confirmed by the fall in the serum acid phosphatase reading. It is difficult to state an expectation of life, but patients live for several years, and the writer knows of one patient who with this treatment is alive eight years after the diagnosis was made. As to possible termination of the disease, severe deterioration from widespread skeletal metastases might occur, or complications affecting the urinary tract, including renal failure.

Effort Syndrome and Thyroid Extract

Q.—*A patient suffering from severe loss of weight and effort syndrome following influenza and several apical abscesses, which were treated, has been given thyroid tablets, ¼ gr. (32 mg.) daily, as a general tonic. Is this sound?*

A.—Thyroid seems to be entirely contraindicated in the circumstances mentioned: it is not a tonic; it increases weight loss; and it might tend to exacerbate the symptoms of effort syndrome, which are often very similar to those of hyperthyroidism. In such a small dose as ¼ gr. daily, however, it would probably do little harm and would hardly have a significant effect upon the heart.

Hepatic Tenderness following Amoebiasis

Q.—*What is the significance of a residual hepatic tenderness following a typical history of amoebic dysentery and hepatitis, treated fully with sulphaguanidine and penicillin; emetine; chiniofon and colonic lavage; and diodoquin? After treatment all examinations, including sigmoidoscopy, proved negative, except for hepatic tenderness, which has not decreased during the last two months. Are agglutination tests now used as criteria of cure in a case such as this?*

A.—The presence of hepatic tenderness in a patient who at some time before has had amoebic dysentery is insufficient in itself to prove that the tenderness is in fact due to amoebiasis. From the data supplied in this particular case it is not possible to say what is the significance of the tenderness. Complement fixation tests have been used by some workers for the diagnosis of amoebiasis, but the results appear so inconsistent that the test should be regarded as experimental, and in the opinion of many it is of little practical value.

Footprints for Identification

Q.—*Can you describe the best method of identifying infants? Is the taking of footprints adequate in this respect?*

A.—Properly recorded footprints would undoubtedly be adequate for the solution of the practical problems of identification which occasionally arise in hospitals, nursing-homes, etc. From time to time a complete system of registration for the entire population has been advocated, including digital, palmar, and plantar prints, but the authorities have never considered that the circumstances warranted the introduction of such a system or that public opinion would be in favour of it.

"Phenadoxone"

Q.—*In prescribing the synthetic analgesic "phenadoxone" is there any danger of addiction? Is this a suitable drug to administer for migraine or for repeated headaches, where an organic basis has been excluded and where tab. codeine co. has proved ineffective?*

A.—Phenadoxone, which now comes under the provisions of the Dangerous Drugs Act, is definitely a drug of addiction, though not to the same extent as morphine, and to a much less extent than diamorphine (heroin). In consequence it is not a very suitable drug for repeated use in the treatment of a recurrent headache or for cases of migraine, for which ergotamine tartrate is a more specific and effective preparation.

Drugs for Raising Blood Pressure

Q.—*Is there any drug which will consistently raise the blood pressure and keep it raised, and, if so, would this prevent vaso-vagal attacks?*

A.—There is no drug which consistently raises the blood pressure and keeps it raised. Sublingual nor-adrenaline, however, is a useful quickly acting pressor agent which may be used to ward off impending vaso-vagal attacks.

NOTES AND COMMENTS

Prescription of P.A.S.—Messrs WARD, BLENKINSOP, AND CO. write: P.A.S. (*para*-aminosalicylic acid) is being increasingly prescribed by doctors for the treatment of pulmonary tuberculosis, but there appears to be some confusion whether *para*-aminosalicylic acid should be dispensed or its equivalent amount in the form of sodium *para*-aminosalicylate dihydrate. One hundred grammes of sodium *para*-aminosalicylate dihydrate, usually referred to as sodium P.A.S., is equivalent to 72.5 g. of *para*-aminosalicylic acid, the accepted abbreviation for which is P.A.S. This compound is in most cases administered orally in the form of flavoured aqueous solutions, and the acid, being relatively insoluble, is not suitable for this purpose. On the other hand, sodium P.A.S. dissolves readily in water and aqueous solutions can easily be prepared.

It would therefore be helpful to pharmacists if this compound was prescribed in doses of the sodium salt—i.e., sodium P.A.S.—and not as P.A.S. unless the acid itself is specifically required. Furthermore, on storage aqueous solutions of sodium P.A.S. darken in colour due to oxidation, and to a lesser degree decarboxylation may take place with the liberation of *meta*-aminophenol, resulting in a rise in *p*H. Although the loss in potency of these solutions is not serious when stored for up to three months in well-filled, tightly closed containers in a cool place, it would be advisable for prescriptions to bear an indication that not more than one week's supply of solution should be prepared at a time. Alternatively, sodium P.A.S. may be prescribed in packets containing individual doses. The patient then dissolves in water the contents of a packet at prescribed intervals and drinks the freshly prepared solution.

Gowers's Syndrome.—Dr. K. M. HAY (Birmingham) writes: I was interested in the remarks on Gowers's syndrome in "Any Questions?" (May 13, p. 1156). I admit to being ignorant of the original description of the syndrome, and I have missed the recent references to it in the *Journal*. However, I have recently come across several patients subject to attacks of weakness, with facial pallor, cold perspiration, and usually headaches in addition. Glucose aborts the attacks, which may recur if not followed up within an hour or so by other food to maintain the blood sugar. We caught one boy of 11 years in an attack with a blood sugar of 57 mg. per 100 ml., and he recovered quickly with glucose. Some days later we attempted to induce a hypoglycaemia by exercising him on an empty stomach, and followed this up with a glucose tolerance test. All readings were well within the bounds of normality. We have collected some data on a number of these cases, but not enough to do more than offer this idea as a suggestion. There is reason to believe that these hypoglycaemic symptoms can occur in those so predisposed in conditions of chronic fatigue. It is probable that mild symptoms of hypoglycaemia are commoner than is realized. In spite of canteens and numerous tea interludes quite a few people can be found who do strenuous work for up to six hours or more without taking any food. Needless to say the syndrome is rare in those offices where tea intervals are frequent. Such a theory would not explain the case mentioned in the question. Would it be possible that for some reason or other something akin to the dumping syndrome is responsible for the symptoms described in this patient?

Correction.—In the article entitled "A Newly Discovered Portrait of William Harvey" (May 27, p. 1259) we omitted to give the price of *The Portraiture of William Harvey*. It is 25s.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology, Westcent, London*. ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone.
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